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[Intervention Review]

Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

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ABSTRACT

Background

Millions of children are hospitalised due to respiratory syncytial virus (RSV) infection every year. Treatment is supportive, and current therapies (e.g. inhaled bronchodilators, epinephrine, nebulised hypertonic saline, and corticosteroids) are ineffective or have limited effect. Respiratory syncytial virus immunoglobulin is sometimes used prophylactically to prevent hospital admission from RSV-related illness. It may be considered for the treatment of established severe RSV infection or for treatment in an immunocompromised host, although it is not licenced for this purpose. It is unclear whether immunoglobulins improve outcomes when used as a treatment for established RSV infection in infants and young children admitted to hospital.

Objectives

To assess the effects of immunoglobulins for the treatment of RSV-proven lower respiratory tract infections in children aged up to three years, admitted to hospital.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, Ovid MEDLINE, Embase, CINAHL, and Web of Science (from inception to 6 November 2018) with no restrictions. We searched two trial registries for ongoing trials (to 30 March 2018) and checked the reference lists of reviews and included articles for additional studies.

Selection criteria

Randomised controlled trials comparing immunoglobulins with placebo in hospitalised infants and children aged up to three years with laboratory-diagnosed RSV lower respiratory tract infection.

Data collection and analysis

Two review authors independently selected trials, assessed risk of bias, and extracted data. We assessed evidence quality using GRADE.

Main results

We included seven trials involving 486 infants and children aged up to three years. The immunoglobulin preparations used in these trials included anti-RSV immunoglobulin and the monoclonal antibody preparations palivizumab and motavizumab. We assessed the primary outcomes of mortality, length of hospital stay, and adverse events as providing low- or very low-certainty evidence due to risk of bias and imprecision. All trials were conducted at sites in high-income countries (USA, Chile, New Zealand, Australia), with two studies including a site in a middle-income country (Panama). Five of the seven studies were "supported" or "sponsored" by the trial drug manufacturers.

We found no evidence of a difference between immunoglobulins and placebo for mortality (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.14 to 5.27; 3 trials; 196 children; 4 deaths; 2 deaths amongst 98 children receiving immunoglobulins, and 2 deaths amongst 98 children receiving placebo. One additional death occurred in a fourth trial, however, the study group of the child was not known and the data were not included in the analysis; very low-certainty evidence), and length of hospitalisation (mean difference −0.70, 95% CI −1.83 to 0.42; 5 trials; 324 children; low-certainty evidence). There was no evidence of a difference between immunoglobulins and placebo in adverse events of any severity or seriousness (reported in five trials) or serious adverse events (four trials) (RR for any severity 1.18, 95% CI 0.78 to 1.78; 340 children; low-certainty evidence, and for serious adverse events 1.08, 95% CI 0.65 to 1.79; 238 children; low-certainty evidence).

We found no evidence of a significant difference between immunoglobulins and placebo for any of our secondary outcomes. We identified one ongoing trial.

Authors' conclusions

We found insufficient evidence of a difference between immunoglobulins and placebo for any review outcomes. We assessed the evidence for the effects of immunoglobulins when used as a treatment for RSV lower respiratory tract infection in hospitalised infants and young children as of low or very low certainty due to risk of bias and imprecision. We are uncertain of the effects of immunoglobulins on these outcomes, and the true effect may be substantially different from the effects reported in this review. All trials were conducted in high-income countries, and data from populations in which the rate of death from RSV infection is higher are lacking.

PLAIN LANGUAGE SUMMARY

Drug treatment for respiratory syncytial virus lung infections

Review question

Does the use of immunoglobulins in very young children hospitalised with a respiratory syncytial virus (RSV) lung infection reduce deaths and hospital stay without increased adverse events, compared with placebo (a similar-appearing fake drug that has no effect)?

Background

Respiratory syncytial virus is a common virus that can infect lungs and airways. Millions of children are treated in hospital each year for RSV, which can result in severe illness and death. The majority of these deaths occur in low-income countries. In high-income countries, the majority of deaths associated with RSV lung infection occur in infants and young children with other illnesses.

Immunoglobulins, also known as antibodies, are a type of molecule normally produced by white blood cells when an infection is present. Immunoglobulins may recognise and attach to viruses (such as RSV) and help destroy them. Immunoglobulins can be produced artificially and given to children who are not making their own RSV antibodies. Some studies have shown that immunoglobulins are helpful in preventing RSV infection in children at high risk of becoming infected. They may also be used as a treatment when an RSV infection is already present, but the effectiveness and safety of immunoglobulins for this use is unknown.

Search date

We searched for evidence up to 6 November 2018.

Study characteristics

We included seven randomised controlled trials (studies in which participants are assigned to one of two or more treatment groups using a random method) that compared the effects of immunoglobulins with placebo in 486 young children hospitalised with RSV

lung infections. All trials were conducted at sites in the USA; three trials included some children from South American countries (Chile and Panama); and one trial also included children from New Zealand and Australia. The trials were published between 1987 and 2014.

Study funding sources

Five trials were supported by the manufacturer of the immunoglobulin tested in the studies. One trial was supported by a government agency, and one trial did not describe how it was funded.

Key results

Immunoglobulins did not appear to be more effective than placebo in preventing deaths among young children with RSV infection, although few deaths occurred in the trials. Immunoglobulins given to children hospitalised with RSV lung infection did not decrease the time spent in hospital. Children treated with immunoglobulins experienced adverse effects of any severity or seriousness and adverse effects considered to be serious (such as respiratory failure) as often as children treated with placebo. There was no difference between immunoglobulins and placebo for any other outcomes measured in the trials, such as the need for oxygen or admission to the intensive care unit. Data from populations in which the rate of death from RSV infection is higher are lacking.

Quality of the evidence

The quality of the evidence was low or very low, which means that the true effect of immunoglobulin treatment for young children in hospital with RSV lung infection may be very different from the findings of this review.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Immunoglobulins compared to placebo for treatment of respiratory syncytial virus infection

Patient or population: children with respiratory syncytial virus infection
Setting: hospital
Intervention: immunoglobulins
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with immunoglobulins				
Mortality follow-up: range 30 days to 60 days	20 per 1000	18 per 1000 (3 to 108)	RR 0.87 (0.14 to 5.27)	196 (3 RCTs)	⊕◯◯◯ VERY LOW [1]	Interventions: monoclonal immunoglobulin palivizumab in 2 trials, titres of neutralising antibodies to RSV in 1 trial Settings: study sites in high-income country (USA) and middle-income country (Panama)
Length of hospitalisation (days) follow-up: range 30 days to 60 days	Mean length of hospitalisation range 5 to 12 days	MD 0.7 fewer (1.83 fewer to 0.42 more)	-	324 (5 RCTs)	⊕⊕◯◯ LOW [2]	Interventions: monoclonal immunoglobulin palivizumab in 2 trials, monoclonal immunoglobulin motavizumab in 1 trial, titres of neutralising antibodies to RSV in 2 trials Settings: study sites in high-income coun-

						tries (USA, Chile) and middle-income country (Panama)
Adverse events follow-up: range 30 days to 90 days	413 per 1000	488 per 1000 (322 to 736)	RR 1.18 (0.78 to 1.78)	340 (5 RCTs)	⊕⊕◯◯ LOW [3]	Interventions: monoclonal immunoglobulin palivizumab in 2 trials, monoclonal immunoglobulin motavizumab in 2 trials, titres of neutralising antibodies to RSV in 1 trial Settings: study sites in high-income countries (USA, Chile, New Zealand, Australia) and middle-income country (Panama)
Serious adverse events follow-up: range 30 days to 90 days	202 per 1000	218 per 1000 (131 to 362)	RR 1.08 (0.65 to 1.79)	238 (4 RCTs)	⊕⊕◯◯ LOW [3]	Interventions: monoclonal immunoglobulin palivizumab in 2 trials, monoclonal immunoglobulin motavizumab in 2 trials Settings: study sites in high-income countries (USA, Chile, New Zealand, Australia) and middle-income country (Panama)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
__CI:__ confidence interval; __MD:__ mean difference; __RCT:__ randomised controlled trial; __RR:__ risk ratio; __RSV:__ respiratory syncytial virus

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded to very low due to serious risk of bias (unclear random sequence generation, selective reporting, and other bias) and very serious imprecision (very small sample size compared to the optimal information size, few events, and wide confidence interval overlapping zones of no effect as well as potential harm or benefit).

[2]Downgraded to low due to serious risk of bias (unclear random sequence generation, selective reporting, and other bias) and serious imprecision.

[3]Downgraded to low due to serious risk of bias (unclear random sequence generation, selective reporting, and other bias) and serious imprecision (small sample size compared to the optimal information size and wide confidence intervals overlapping zones of no effect as well as potential harm or benefit).

BACKGROUND

Description of the condition

The respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infections (LRTI), such as bronchiolitis and pneumonia, in infancy and childhood (Nair 2010). Nearly all children will have been infected with RSV by the age of two years (Greenough 2001). Respiratory syncytial virus infection carries a substantial disease burden, with 33 million (uncertainty range 22 to 50 million) episodes of RSV-associated acute LRTI globally in 2015, resulting in about three million hospital admissions and approximately 59,000 deaths (Shi 2017). The societal burden associated with caring for the ill and healthcare costs due to RSV infection are substantial (Langley 1997; Paramore 2004). The clinical manifestations of RSV infection vary according to age and health status. Amongst children aged over three years and adults, RSV causes only mild acute respiratory symptoms (such as common cold, sore throat, headache, cough, low-grade fever, and malaise) (Mayo Clinic 2017). However, about 20% to 30% of younger children presenting with these symptoms can progress rapidly to diffuse small airways disease with low-grade fever, cough, wheezing, shortness of breath, decreased oral intake, and diffuse crackles/rales on chest auscultation (American Academy of Pediatrics 2015). Infants aged up to six weeks may present with a non-specific sepsis-like picture (Oray-Schrom 2003). Apnoea (transient period of breathing cessation) may also be present in these infants (Ralston 2009). Severe cases of RSV infection in young children and infants can cause oxygen starvation (hypoxia) and acute respiratory (ventilatory) failure, which may need mechanical ventilation in an intensive care unit. Most children with RSV infection make a full recovery, but some develop an increased risk of wheezing, asthma, and impaired lung function later in life (Zomer-Kooijker 2014).

Treatment of acute RSV infection is primarily supportive, and includes suction to remove airways secretions, administration of supplemental oxygen, and fluid replacement (American Academy of Pediatrics 2018). Interventional agents are largely ineffective or of limited effectiveness. The evidence for inhaled bronchodilator therapy with beta-agonists is unconvincing for bronchiolitis (Gadomski 2014), and there is insufficient evidence to support the use of epinephrine for the treatment of bronchiolitis amongst children admitted to hospital (Hartling 2011). Hypertonic saline and corticosteroids are also used. Nebulised hypertonic saline solution has a modest effect on length of hospital stay amongst infants hospitalised with acute bronchiolitis (Zhang 2017), and systemic or inhaled glucocorticoids have not been found to be effective for this condition (Fernandes 2013). The effects of the antiviral therapy ribavirin in children with respiratory infections caused by RSV are unclear, and ribavirin is currently reserved for immunosuppressed children with severe RSV infection (American Academy of Pediatrics 2018). The World Health Organization (WHO) has targeted RSV for vaccine development (Broadbent 2015).

Description of the intervention

Immunogloblin therapy involves the administration of preparations containing high levels of immunoglobulins, or antibodies. Administration of these antibodies confers passive resistance to infection by increasing the quantity or quality of antibodies the individual possesses. Immunoglobulin therapy may also be used to reduce the severity of symptoms of disease in autoimmune disorders (e.g. Guillain-Barre syndrome), secondary immunodeficiencies (e.g. HIV), and acute infections (Jolles 2005). Immunoglobulin preparations for RSV contain high concentrations of antibodies against RSV. These can be pooled preparations, whereby the preparation is derived from the plasma of donors with naturally high circulating levels of RSV neutralising antibodies. These preparations also contain neutralising antibodies to other viruses and bacteria. Alternatively, the preparation can comprise humanised monoclonal antibodies directed only against the RSV-F fusion protein expressed on the surface of the RSV viron (Griffiths 2017).

Palivizumab (Synagis, MedImmune) is a monoclonal antibody preparation administered as an intramuscular injection (Synagis 2017). It was approved by the US Food and Drug Administration (FDA) for RSV prophylaxis of high-risk children in 1998, and has since received approval in over 45 other countries (Resch 2017). In randomised controlled trials, palivizumab reduced hospitalisations for RSV in children with congenital heart disease (risk ratio reduction (RRR) 0.45) (Feltes 2003), prematurity (RRR 0.78), and bronchopulmonary dysplasia (RRR 0.39). The American Academy of Pediatrics recommends immunoglobulin prophylaxis for high-risk infants and children (American Academy of Pediatrics 2014). Recommendations for palivizumab prophylaxis differ globally because of its high cost (USD 3000 to 5000 per child per year) (Wang 2011). Palivizumab is not licenced for the treatment of established RSV infection. However, it has nonetheless been used to treat children with severe infection or to prevent progression of the disease (Hu 2010; Turner 2014).

In 1996, RSV immune globulin intravenous (RSV-IGIV, RespiriGam, MedImmune) was approved by the FDA for use in the prevention of severe RSV infections in infants and children aged up to 24 months with bronchopulmonary dysplasia or history of premature birth following two randomised controlled trials in these high-risk infants. RSV-IGIV administered monthly during the RSV season resulted in a 40% to 65% reduction in hospitalisation rates (Groothuis 1993; PREVENT 1997). RSV-IGIV was superseded by palivizumab in 2004.

Motavisumab is a monoclonal antibody against RSV that was derived from palivizumab in the early 2000s. It has been reported to offer greater potency against RSV in animal studies (Mejías

2005). However, its development was discontinued in 2010 after the FDA declined the manufacturer's request for licensure due to concerns about safety and non-inferiority to palivizumab.

How the intervention might work

Immunoglobulins provide passive immunity when the antibodies bind and neutralise viral proteins responsible for viral attachment to cells (G protein) and cell fusion (F protein) (Roche 2003), which reduces viral replication (Rodriguez 1997). Palivizumab is a humanised monoclonal antibody specific for the envelope fusion protein (RS-F) of RSV. As viruses need to fuse with living cells to replicate, this would reduce viral replication in the lungs of those infected with RSV.

Why it is important to do this review

Therapy for RSV infection of the lower respiratory tract in children is primarily supportive, with existing interventional agents not generally recommended or indicated. Although immunoglobulins are currently licenced for the prevention of RSV LRTI only, they may also be used as a management strategy. As such, an assessment of the efficacy and safety of immunoglobulins as a treatment for established RSV infection in children was necessary.

OBJECTIVES

To assess the effects of immunoglobulins for the treatment of RSV-proven LRTIs in children aged up to three years, admitted to hospital.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that compared immunoglobulin treatment with a placebo control.

Types of participants

Infants and children (aged up to three years) hospitalised for bronchiolitis, pneumonia, or other LRTI with laboratory-documented RSV infection.

Types of interventions

Treatments involving infusions with immunoglobulins. We did not apply any limits regarding immunoglobulin type, dose, or method of administration. The comparator was placebo.

Types of outcome measures

Primary outcomes

1. Mortality from any cause occurring during hospitalisation or follow-up.
2. Length of hospitalisation.
3. Adverse events. We used definitions applied by study investigators for adverse events and serious adverse events. These were:

i) adverse events: the number of participants experiencing one or more adverse event of any severity or seriousness during the trial or follow-up. Adverse events were any adverse changes from baseline occurring after study drug administration. These events may or may not have been related to the study drug; and

ii) serious adverse events: the number of participants experiencing one or more adverse events considered by study investigators to be serious in nature. These were events that resulted in a substantial impairment of baseline function or death, required or prolonged hospitalisation, or were otherwise considered an important medical event, during the trial or follow-up.

Secondary outcomes

1. Need for mechanical ventilation (for participants in studies where requirement for mechanical ventilation was not a study entry criterion).
2. Duration of mechanical ventilation (for those ventilated).
3. Need for supplemental oxygen.
4. Duration of supplemental oxygen (for those receiving supplemental oxygen).
5. Need for intensive care unit (ICU) admission.
6. Duration of stay in the ICU (for those admitted to the ICU).
7. Pulmonary function measured by spirometry.
8. Rehospitalisation for recurrent breathing difficulties in the long term.
9. The occurrence of reactive airway disease in the long term.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (Issue 10, October 2018 accessed 6 November 2018) in the Cochrane Library, which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, Ovid MEDLINE (1946 to 6 November 2018), Embase (Elsevier) (1974 to 6 November 2018), CINAHL (EBSCO) (1982 to 6 November 2018), and Web of Science (Clarivate Analytics) (1985 to 6 November 2018). There were no language restrictions.

We used the search strategy in Appendix 1 to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search Embase (Appendix 2), CINAHL (Appendix 3), and Web of Science (Appendix 4).

Searching other resources

We searched two trials registers (US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/)) for completed and ongoing trials on 30 March 2018. We conducted a forward citation search of included studies via Web of Science on 30 March 2018. We also searched the reference lists of included trials and relevant review articles.

Data collection and analysis

Selection of studies

Two review authors (SLS and one of the current review authors (CDM or MD) or one of two review authors who worked on an earlier draft of the review, (MK or MG)) independently screened titles and abstracts. We retrieved full-text study reports of titles and abstracts considered by two review authors to be potentially relevant. Two review authors (SLS and either CDM or MD or MK or MG) independently screened the retrieved full-text reports to identify studies for inclusion, and recorded the reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion or by consultation with a third review author (either CDM or MD) when necessary.

Data extraction and management

Two review authors (SLS and CDM or MK) independently extracted the following data from the included studies: study design and setting; location of study, inclusion and exclusion criteria, and characteristics of the participants; characteristics of the intervention and comparison (type of immunoglobulin, dosage, method of administration); and the primary and secondary outcomes specified and time points reported. Disagreements regarding data extraction were resolved by discussion. One review author (SLS) entered data into RevMan 5 (Review Manager 2014). Two other review authors (SA and MH) verified data extraction and entry.

Assessment of risk of bias in included studies

Two review authors (SLS and MD or CDM) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Disagreements were resolved by discussion with a third review author (MD or CDM). We considered the following seven domains in our 'Risk of bias' assessment.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias including bias related to study funding sources.

We assessed each study as being at low, high, or unclear risk of bias for each domain and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. For other bias relating to study funding sources, we rated a study as at high risk of bias if the report indicated that it was funded, supported, or sponsored by parties that may have had a vested interest in the results of the study (e.g. drug manufacturer). We rated studies as at unclear risk of bias if study authors or members of the study group had potential conflicts of interest (e.g. were employees of the drug manufacturer). We took into account the risk of bias for the studies contributing to each outcome when considering treatment effects.

Measures of treatment effect

We used Cochrane's Review Manager 5 (RevMan 5) software for all analyses (Review Manager 2014). We planned to calculate risk ratios (RRs) and 95% confidence intervals (CIs) for binary outcomes (i.e. mortality and adverse events). For continuous outcomes, such as length of hospitalisation, we calculated the mean difference (MD) and 95% CIs.

Unit of analysis issues

The participant was the unit of analysis in our meta-analysis. We planned to apply any corrections for clustering as described in the *Cochrane Handbook for Systematic Reviews of Interventions* if the unit of randomisation was not the same as the unit of analysis in cluster-randomised trials (Higgins 2011).

Dealing with missing data

For continuous outcomes where no standard deviations (SD) were reported, we obtained them from standard errors for group means using the method specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For continuous outcomes where median was reported instead of the group mean, we described outcomes for that study narratively for each outcome (see Results). For the primary outcome, length of hospital stay, where median was reported instead of group mean, we used the median and range to calculate a mean and SD employing the method of Hozo (Hozo 2005). The study was then included in the meta-analysis in a post hoc sensitivity analysis.

Assessment of heterogeneity

We assessed the presence of clinical heterogeneity by comparing populations (age, immune status, severity of disease), interventions, and outcomes before deciding whether it was appropriate to pool data. We planned to describe studies that we judged to be too clinically heterogeneous and not combine them in a meta-analysis. We assessed studies providing data on each outcome without substantial clinical heterogeneity for statistical heterogeneity by means of the I^2 statistic (I^2 greater than 50% was considered substantial heterogeneity) (Higgins 2011).

Assessment of reporting biases

We planned to assess publication bias using a funnel plot test if more than 10 studies contributed data. However, there were too few included studies to enable this assessment.

Data synthesis

We pooled outcome data from studies that we judged to be clinically homogeneous using RevMan 5 (Review Manager 2014). As we considered that a single true effect was not plausible due to variation in populations and interventions, we pooled study data using a random-effects model.

For studies with more than one placebo or intervention group, we combined data according to the formula in Section 7.7.3.8 Combining groups of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We planned to report the number of participants who experienced one or more adverse events (whether the event was considered serious or not, or whether the event was attributed by the investigators to the study interventions or not) rather than the number of adverse events.

GRADE and 'Summary of findings' table

We created Summary of findings for the main comparison for the following outcomes: mortality, length of hospitalisation, adverse events, and serious adverse events. We assessed the certainty of the evidence for each outcome included in the 'Summary of findings' table using the GRADE evidence grading system as described in the *GRADE Handbook*, Schünemann 2013, and Section 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used GRADEpro GDT software (GRADEpro GDT). We took the following factors into consideration when deciding whether or not to downgrade the certainty of evidence for each outcome: risk of bias, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias.

We considered the number of events, the size of the confidence intervals and calculated a posteriori the optimal information size to assess imprecision. We considered a difference of 25% as the minimal clinically important difference for dichotomous outcomes to determine optimal information size (this is the threshold recommended by GRADE when there is no compelling rationale for an alternate threshold) (Schünemann 2013). For the continuous outcome length of stay, we considered one day as the minimum clinically important difference (the judgement that reductions in stay of one day are clinically important was based on the clinical experience of the review authors and agreed upon through discussion). Calculation of the optimal information size depends upon this difference and the resulting sample size required (Schünemann 2013). We assumed a 3% risk of mortality (median control event rate from trials providing these data); 30% risk of adverse event (median control event rate from trials providing these data); and an SD of 6.4 (median control SD from trials providing these data) with a power of 80% and a two-sided alpha of 0.05. One review author (SLS) initially applied the GRADE criteria and then discussed the certainty of evidence ratings with other review authors (CDM, MD). Final decisions on the ratings were reached through discussion and consensus. We justified all decisions to downgrade the certainty of studies in table footnotes.

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following subgroup analyses.

1. Children aged six months or less versus children older than six months.
2. Children with a recurrent episode of RSV versus first episode.
3. Immunocompromised versus non-immunocompromised children.
4. Children with congenital heart disease.
5. Children with bronchopulmonary dysplasia.
6. Palivizumab versus other immunoglobulin preparations.

However, the small number of included studies precluded these analyses.

Sensitivity analysis

We planned to perform sensitivity analyses to assess the impact of excluding studies at high risk of bias for allocation concealment based on the 'Risk of bias' assessment for the primary outcome

estimates. However, all studies were judged to be at either low or unclear risk of bias for allocation concealment, so sensitivity analysis was not performed.

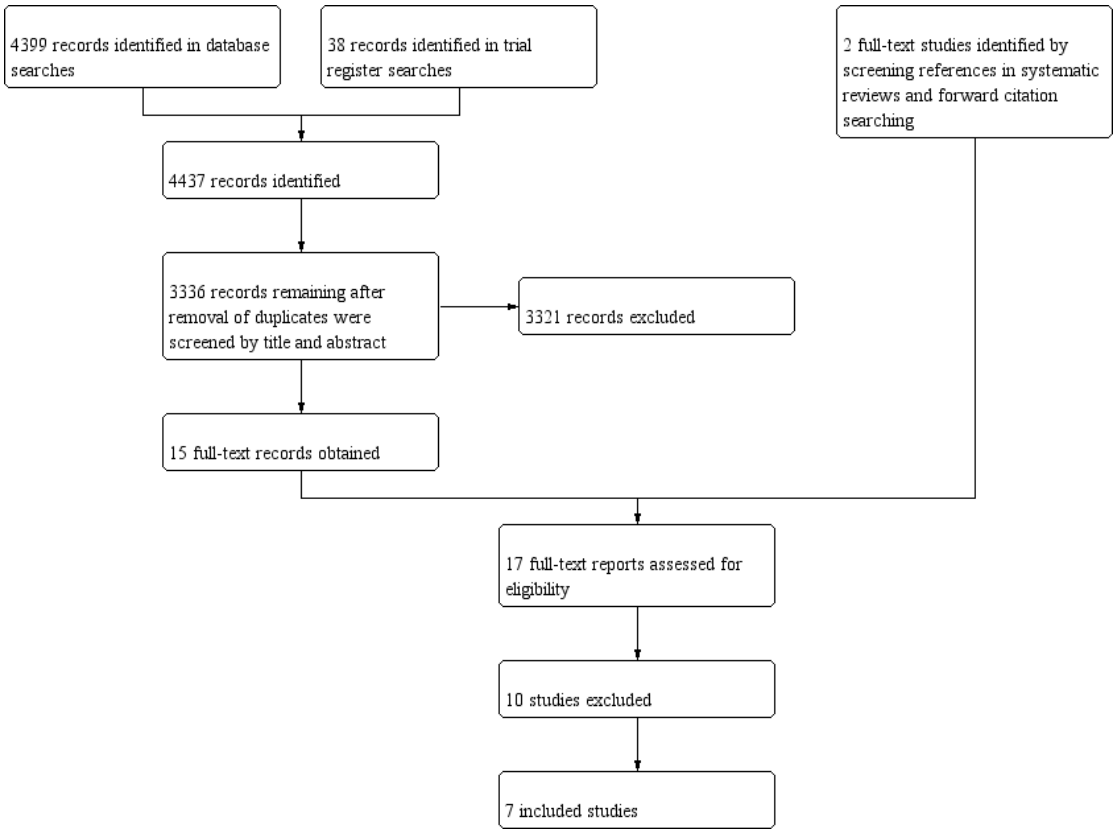
RESULTS

Description of studies

Results of the search

Database searches (conducted 6 November 2018) yielded 4399 records, and 38 records were identified in trials register searches (conducted 30 March 2018). We screened 3336 records for eligibility after removal of duplicates, of which 15 were retrieved for full-text screening. We also obtained two additional records identified from screening reference lists of previously published reviews and forward citation searching the included studies for full-text screening. We therefore screened 17 full-text records, and included seven studies in the review (Hemming 1987; Lagos 2009; Malley 1998; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b; Sáez-Llorens 2004). We identified one ongoing study (NCT02442427). A flow diagram of the study selection process is presented in Figure 1.

Figure 1. Study flow diagram.



Included studies

A full description of all seven included studies is provided in Characteristics of included studies.

Design

All seven included studies were RCTs that used a parallel-group design. Three trials compared two or more different doses of the in-

tervention with placebo (Lagos 2009; Ramilo 2014; Sáez-Llorens 2004), with escalation to a higher dose after a specified period of time in the absence of toxicity or serious adverse events in two studies (Lagos 2009; Sáez-Llorens 2004).

Participants

A total of 486 children were included in the seven trials; the number of children per trial ranged from 31 to 118. All trials were conducted at sites in high-income countries, with two trials including a study site in a middle-income country (Panama). Six trials were conducted in the USA (Hemming 1987; Lagos 2009; Malley 1998; Rodriguez 1997a; Rodriguez 1997b; Sáez-Llorens 2004); two of these studies had sites in South America (Sáez-Llorens 2004 in Panama and Lagos 2009 in Chile). One trial was reported to have been conducted at "multiple sites", which included the USA, New Zealand, Chile, Panama, and Australia (Ramilo 2014).

The studies included children and infants hospitalised for pneumonia, bronchiolitis, or other LRTI with a documented positive RSV test. Participants were described as "previously healthy" in five studies (Hemming 1987; Lagos 2009; Ramilo 2014; Rodriguez 1997b; Sáez-Llorens 2004); at "high risk for severe RSV infections" in one study (Rodriguez 1997a); and were a mix of previously healthy children and children with "chronic medical conditions" in one study (Malley 1998). High-risk infants included those with severe bronchopulmonary dysplasia, chronic lung disease, congenital heart disease, or prematurity (< 32 weeks gestational age). One study included only children who required intubation and mechanical ventilation at study entry (Malley 1998), and another study included children who required more than 30% supplemental oxygen (Sáez-Llorens 2004). Participants were aged up to 12 months in one study (Ramilo 2014); up to two years at randomisation in five studies (Lagos 2009; Malley 1998; Rodriguez 1997a; Rodriguez 1997b; Sáez-Llorens 2004); and one study did not report an upper age limit, but included children with body weight up to 10 kg (Hemming 1987).

Interventions

The included studies evaluated different doses and types of immunoglobulin preparations. Three studies used titres of neutralising antibody to RSV administered intravenously (Hemming 1987; Rodriguez 1997a; Rodriguez 1997b), at doses of 1500 mg per kg of body weight in Rodriguez 1997b and Rodriguez 1997a and 2 g per kg of body weight in Hemming 1987. The monoclonal immunoglobulin motavizumab was administered intravenously in two studies at doses of 3 mg, 15 mg, or 30 mg per kg of body weight in Lagos 2009 and at doses of 30 mg or 100 mg per kg of body weight in Ramilo 2014. The monoclonal immunoglobulin palivizumab was administered intravenously at doses of 5 mg and 15 mg per kg in one study (Sáez-Llorens 2004), and at doses of 15 mg per kg in another study (Malley 1998).

Placebo was normal saline (0.9% sodium chloride) or half-normal saline (0.45%) in three studies, Lagos 2009; Malley 1998; Sáez-Llorens 2004, and albumin (0.5% or 6%) in three studies (Hemming 1987; Rodriguez 1997a; Rodriguez 1997b). The composition of the placebo was not stated in one study (Ramilo 2014). None of the studies provided detail on who was involved in delivering the interventions to participants. Only two studies with multiple study sites within the same country stated that "methods were standardized for all centres" (Rodriguez 1997a; Rodriguez 1997b).

Outcome measures

Four studies reported that deaths occurred during the trial or the follow-up period (Hemming 1987; Malley 1998; Rodriguez 1997a; Sáez-Llorens 2004). All seven included studies reported the duration of hospitalisation. Six studies reported the number of adverse events that occurred in the study groups (Lagos 2009; Malley 1998; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b; Sáez-Llorens 2004). Five of six studies that involved children who did not require mechanical ventilation at study entry reported the need for mechanical ventilation (Hemming 1987; Lagos 2009; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b). Five studies reported the duration of mechanical ventilation (Lagos 2009; Malley 1998; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b). Four of five studies involving children who did not require intubation, mechanical ventilation, or supplemental oxygen at study entry reported the need for supplemental oxygen (Hemming 1987; Lagos 2009; Ramilo 2014; Rodriguez 1997a). Five studies reported duration of supplemental oxygen (Hemming 1987; Lagos 2009; Malley 1998; Ramilo 2014; Sáez-Llorens 2004). Five of six studies involving children not in the ICU reported the need for admission to the ICU (Hemming 1987; Lagos 2009; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b), and four studies also reported the duration of stay in the ICU (Lagos 2009; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b). Two studies reported on rehospitalisations for recurrent breathing difficulties in the long term (Rodriguez 1997a; Rodriguez 1997b).

No studies reported on the outcomes of pulmonary function or the occurrence of reactive airway disease in the long term.

Excluded studies

We excluded 10 study reports from the review: six were reviews (AAP 1998; Faber 2008; Givner 1999; Harkensee 2006; Hu 2010; Wegzyn 2014); three were prophylaxis rather than treatment studies (Feltes 2011; Fernández 2010; Halsey 1997); and one study did not randomise participants to immunoglobulin and control groups (Helmink 2016). See Characteristics of excluded studies.

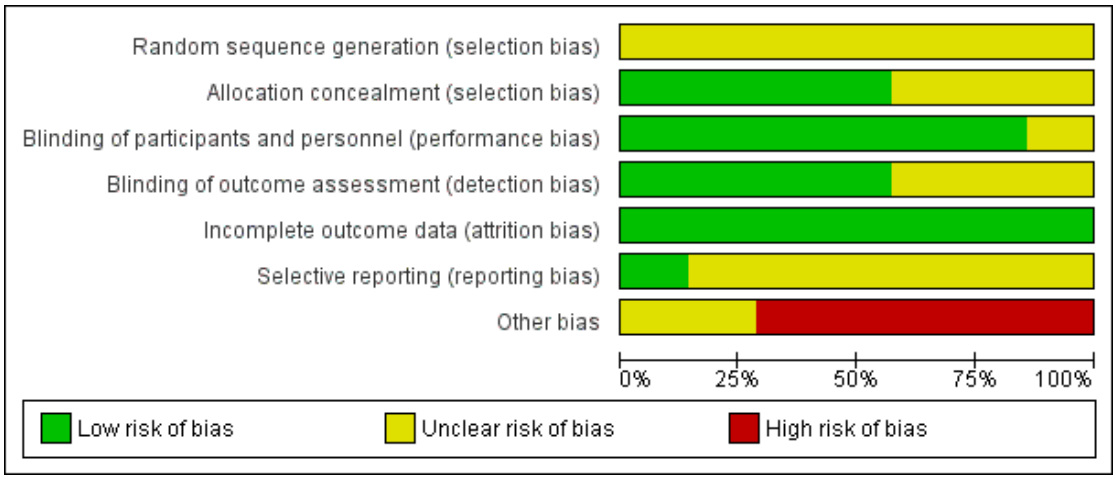
Ongoing studies

We identified one ongoing study (NCT02442427). This study included children aged up to three years presenting to an emergency department with acute bronchitis and positive RSV antigen test. The children were randomised to receive either a single intravenous dose of palivizumab or an identical saline placebo. The primary outcome is readmission within three weeks of discharge.

Risk of bias in included studies

A summary of the 'Risk of bias' assessment is presented in Figure 2. Risk of bias was unclear for random sequence generation in all studies. Risk of bias was mostly low for allocation concealment, blinding, and incomplete outcome data. Risk of bias from selective reporting was unclear in most studies. We assessed all studies as at unclear or high risk of other bias due to study funding sources and potential author conflicts of interest.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

None of the included studies adequately described the method used to generate the randomisation sequence. Four included studies reported and used appropriate methods to conceal the allocation sequence and were rated as at low risk of bias for this domain (Malley 1998; Ramilo 2014; Rodriguez 1997a; Sáez-Llorens 2004). The method of concealing the allocation sequence was unclear in three studies (Hemming 1987; Lagos 2009; Rodriguez 1997b).

Blinding

We rated six studies as at low risk of performance bias because appropriate steps were taken to ensure blinding of participants and personnel (e.g. identical intervention and placebo solutions) (Hemming 1987; Malley 1998; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b; Sáez-Llorens 2004). We could not determine the adequacy of blinding of participants and personnel in one study, which we assessed as at unclear risk of bias (Lagos 2009). We rated the risk of detection bias as low for clinical outcomes in four studies (Malley 1998; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b). There was insufficient information in three studies to determine the risk of detection bias, although this was unlikely

to impact objective outcomes such as mortality or length of stay (Hemming 1987; Lagos 2009; Sáez-Llorens 2004). We assessed these studies as at unclear risk of bias.

Incomplete outcome data

All included studies either had no losses to follow-up or exclusions, or had a small amount of attrition that was deemed unlikely to bias the results. We assessed all included studies to be at low risk of attrition bias (Hemming 1987; Lagos 2009; Malley 1998; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b; Sáez-Llorens 2004).

Selective reporting

We assessed only one study as at low risk of reporting bias, which provided outcome data for all outcomes specified in the trial protocol (Ramilo 2014). In five studies (Lagos 2009; Malley 1998; Rodriguez 1997a; Rodriguez 1997b; Sáez-Llorens 2004), the risk of reporting bias was unclear because data were reported for the outcomes specified in the methods section of the publication, but none of the studies had an available trial protocol. It was therefore unclear whether other outcomes were measured but not reported based on the results. Outcomes of interest were not specified in the methods section of one study (Hemming 1987).

Other potential sources of bias

We judged all seven included studies to be at unclear or high risk of other potential bias. Five studies either received financial "support" from or were "sponsored" by the intervention manufacturer to conduct the study. In the remaining two studies, study authors or members of the study group were employees of or had received funding from the manufacturer.

Effects of interventions

See: **Summary of findings for the main comparison** Immunoglobulins compared to placebo for treatment of respiratory syncytial virus infection

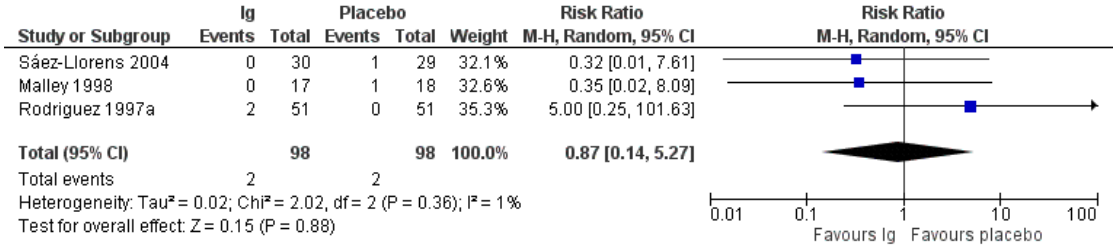
See Summary of findings for the main comparison for the main comparison intravenous immunoglobulin compared with placebo for RSV infection in infants and children.

Primary outcomes

1. Mortality

Five deaths were reported among 196 children in four included studies (Hemming 1987; Malley 1998; Rodriguez 1997a; Sáez-Llorens 2004). We excluded data from Hemming 1987 from analysis because the study group of the one child who died was not reported. We found no evidence of a difference in mortality between children in the immunoglobulin and placebo groups (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.14 to 5.27; Analysis 1.1; Figure 3; very low-certainty evidence, downgraded due to serious risk of bias and very serious imprecision). In Rodriguez 1997a, two children in the immunoglobulin group died; the deaths were considered by the authors to be unrelated to the administration of immunoglobulins (one death occurred after cardiac corrective surgery, and the other was caused by urosepsis in a child with bronchopulmonary dysplasia). Two deaths occurred among children in the placebo group in two studies due to progressive respiratory failure (Malley 1998), possibly complicated by bacterial superinfection (Sáez-Llorens 2004). One child (study group unknown) died in an accident after discharge (Hemming 1987). A breakdown of the numbers of deaths that occurred in the included studies is presented in Table 1.

Figure 3. Forest plot of comparison: Immunoglobulins versus placebo, outcome: 1.1 Mortality.

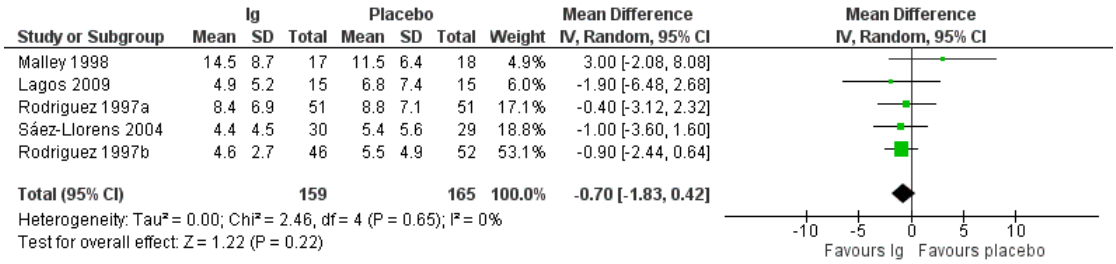


2. Length of hospitalisation

All seven included studies reported on length of hospital stay (in days). However, data from two studies could not be included in the meta-analysis due to missing variability data or missing useable

outcome data (median rather than mean was reported) (Hemming 1987; Ramilo 2014). The length of hospital stay ranged from 4.4 to 14.5 days with immunoglobulins and 4.9 to 7.4 days with placebo. There was no difference in length of hospitalisation (in days) between immunoglobulins and placebo (mean difference (MD) −0.70, 95% CI −1.83 to 0.42; Analysis 1.2, Figure 4; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision).

Figure 4. Forest plot of comparison: Immunoglobulins versus placebo, outcome: 1.2 Length of hospitalisation (days).



In two studies that could not be meta-analysed, the mean length of hospital stay in the treatment and placebo groups was 3.94 days and 3.06 days, respectively, in Hemming 1987, and the median duration of hospitalisation was 3.05 days for the motavizumab 30 mg/kg group, 2.99 days for the motavizumab 100 mg/kg group, and 2.88 days for the placebo group in Ramilo 2014. We conducted a post hoc sensitivity analysis including the study of Ramilo (Ramilo 2014). There was no difference in length of hospitalisation between immunoglobulins and placebo (MD −0.33, 95% CI −1.17 to 0.51).

3. Adverse events

All seven included studies reported on adverse events. Five studies provided data on the number of children who experienced one or more adverse events of any severity or seriousness (Lagos 2009; Malley 1998; Ramilo 2014; Rodriguez 1997a; Sáez-Llorens 2004). Four studies provided data on the number of children who experienced one or more adverse events considered by study investigators to be serious in nature (Lagos 2009; Malley 1998; Ramilo 2014; Sáez-Llorens 2004). Two studies did not provide data, stating only that "there were no serious adverse events associated with RSVIG therapy" in Rodriguez 1997b and "Follow up to date has revealed no harmful effects resulting from immunotherapy of RSV infections" in Hemming 1987.

The numbers of children who experienced one or more adverse events (of any severity) and the number who experienced one or more serious adverse events is presented in Table 2. Table 2 also shows the number of children who experienced one or more adverse events considered by the study investigators to be related to the study drug.

There was no difference between the treatment and placebo groups in the number of children who experienced one or more adverse events of any severity or seriousness (RR 1.18, 95% CI 0.78 to 1.78; Analysis 1.3; Figure 5; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision). There was moderate heterogeneity (I^2 = 57%) amongst trials overall for this analysis. There was no difference between treatment and placebo groups in the number of children who experienced one or more adverse events judged by study investigators to be serious in nature (RR 1.08, 95% CI 0.65 to 1.79; Analysis 1.4; Figure 6; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision).

Figure 5. Forest plot of comparison: Immunoglobulins versus placebo, outcome: 1.3 Adverse events.

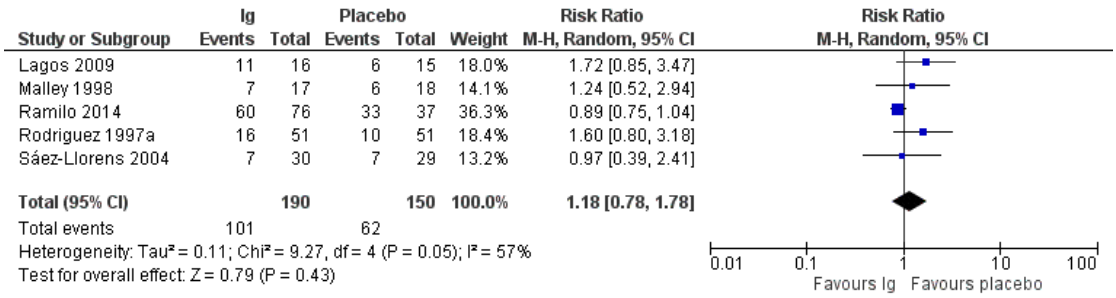
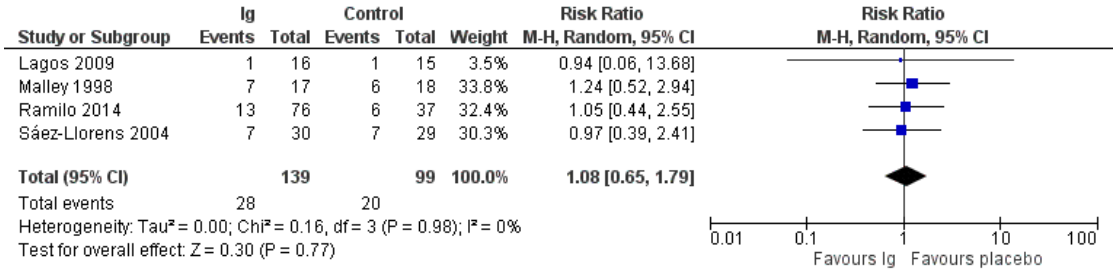


Figure 6. Forest plot of comparison: Immunoglobulins versus placebo, outcome: 1.4 Serious adverse events.



Secondary outcomes

1. Need for mechanical ventilation

Five of six studies that involved children who did not require mechanical ventilation at study entry reported the need for subsequent mechanical ventilation (Hemming 1987; Lagos 2009; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b). Hemming 1987 reported that "Neither group included infants who... needed ventilatory support". This study was therefore not included in the meta-analysis (as per Section 16.9.3 of the *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011). We do not know if there is a difference in the need for mechanical ventilation between children who received immunoglobulins and those who received placebo (RR 1.24, 95% CI 0.64 to 2.41; Analysis 1.5; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision).

2. Duration of mechanical ventilation

Five included studies reported duration of ventilation (in days) (Lagos 2009; Malley 1998; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b). However, data from two studies could not be included in the meta-analysis due to missing useable outcome data (median rather than mean was reported, or there were no variation data) (Lagos 2009; Ramilo 2014). It is unclear if there is a difference in duration of mechanical ventilation between immunoglobulins and placebo (MD −0.22, 95% CI −2.64 to 2.21; Analysis 1.6; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision).

In the two studies excluded from the meta-analysis, the median duration of ventilation was 7.8 days for children in the motavizumab 30 mg/kg group and 4.6 days for children in the motavizumab 100 mg/kg group; no child in the placebo group required mechanical ventilation (Ramilo 2014). In Lagos 2009, one child in the motavizumab 30 mg/kg group required mechanical ventilation for a duration of 16 days. The mean duration of ventilation was five days for two children in the placebo group.

3. Need for supplemental oxygen

Four of five studies that included children who did not require intubation, mechanical ventilation, or supplemental oxygen at study entry reported the need for subsequent supplemental oxygen (Hemming 1987; Lagos 2009; Ramilo 2014; Rodriguez 1997a). Of these studies, two did not provide data but reported that "No significant differences were observed between the intravenous immunoglobulin (IVIG)-treated and the placebo-treated groups in the following: supplemental O_2 requirements..." in Hemming 1987 and "no differences between the respiratory syncytial virus immune globulin (RSVIG) and placebo groups were observed in... supplemental oxygen" in Rodriguez 1997a. We found no evidence of a difference in the need for supplemental oxygen between immunoglobulins and placebo (RR 1.18, 95% CI 0.94 to 1.49; Analysis 1.7; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision).

4. Duration of supplemental oxygen

Five studies reported duration of supplemental oxygen (in days) (Hemming 1987; Lagos 2009; Malley 1998; Ramilo 2014; Sáez-Llorens 2004). However, two of these studies were excluded from the meta-analysis due to missing useable outcome data (Hemming 1987; Ramilo 2014). We found no evidence of a difference in duration of supplemental oxygen between children in the immunoglobulin and placebo groups (MD −0.54, 95% CI −2.26 to 1.17; Analysis 1.8; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision).

In the two studies that could not be included in the meta-analysis, the median duration of supplemental oxygen was 3.0 days for the motavizumab 30 mg/kg and 100 mg/kg groups and the placebo group (Ramilo 2014), and the Hemming 1987 investigators stated that "no significant differences" were observed in supplemental oxygen requirements between children in the intravenous immunoglobulin and placebo groups, but did not provide numerical data.

5. Need for intensive care unit admission

Five studies reported the need for admission to the ICU (Hemming 1987; Lagos 2009; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b). Of these studies, one reported that "Neither group included infants who required admission to an intensive care unit" (Hemming 1987), therefore data from Hemming 1987 were not included in the meta-analysis (as per Section 16.9.3 of the *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011). There was no evidence of a difference in the need for ICU admission between children who received immunoglobulins and those who received placebo (RR 1.22, 95% CI 0.64 to 2.32; Analysis 1.9; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision).

6. Duration of stay in the intensive care unit

Four studies reported duration of stay (in days) in the ICU (Lagos 2009; Ramilo 2014; Rodriguez 1997a; Rodriguez 1997b). However, two studies could not be included in the meta-analysis due to missing useable outcome data (Lagos 2009; Ramilo 2014). There was no evidence of a difference in duration of stay in the ICU between children in the immunoglobulin and placebo groups (MD −2.13, 95% CI −4.55 to 0.30; Analysis 1.10; low-certainty evidence, downgraded due to serious risk of bias and serious imprecision).

In the two studies excluded from the meta-analysis, the median duration of stay in the ICU was 10 days for the motavizumab 30 mg/kg group, 5 days for the motavizumab 100 mg/kg group, with no ICU admissions amongst children in the placebo group (Ramilo 2014). In Hemming 1987, one child in the motavizumab group stayed in the ICU for 16 days; the mean duration of stay amongst children in the placebo group was five days.

7. Pulmonary function

None of the included studies reported pulmonary function or spirometry data.

8. Rehospitalisation for recurrent breathing difficulties in the long term

Two studies reported readmissions during the subsequent respiratory seasons (Rodriguez 1997a; Rodriguez 1997b). In one study, three (of 26) children in the RSV immunoglobulin group were hospitalised for LRTI during the subsequent respiratory season (all three LRTI hospitalisations were due to RSV), and three (of 26) children in the placebo group were hospitalised for LRTI during the subsequent respiratory infections season (two were due to RSV) (Rodriguez 1997b). In the second study, five (of 48) children in the RSV immunoglobulin group were hospitalised for LRTI during the subsequent respiratory infections season (three were due to RSV), and six (of 50) children from the placebo group were hospitalised for LRTI during the subsequent respiratory infections season (three were due to RSV) (Rodriguez 1997a).

9. The occurrence of reactive airway disease in the long term

None of the included studies reported the occurrence of reactive airway disease in the long term. One study reported that the incidence of wheezing (a symptom of reactive airway disease) was similar between children in the motavizumab and placebo groups in the 12 months after randomisation (Ramilo 2014).

Subgroup analyses

We planned to undertake subgroup analyses based on children's age, episode of RSV, type of immunoglobulin intervention, and

existing comorbidities. These analyses were not possible due to lack of data.

Sensitivity analysis

We planned to conduct a sensitivity analysis to examine the effect of risk of bias (from allocation concealment) on outcome estimates. However, none of the included studies were judged to be at high risk of bias for allocation concealment.

DISCUSSION

Summary of main results

We aimed to assess the effectiveness and safety of immunoglobulins as a treatment for RSV-associated LRTIs in hospitalised infants and young children.

We searched the literature to 6 November 2018 and included seven studies (486 children) that met the review inclusion criteria: two studies compared palivizumab to placebo; two studies compared motavizumab to placebo; and three studies compared high RSV neutralising antibody titre immunoglobulin to placebo.

Very low-certainty evidence from three studies (downgraded in the GRADE assessment for risk of bias and imprecision due to small sample size and low event rates) meant that it is unclear if there is a difference between immunoglobulins and placebo in mortality (from any cause during hospitalisation or follow-up). Wide confidence intervals around the estimate did not rule out a null effect or potential harm from immunoglobulin treatment.

Low-certainty evidence from five studies (downgraded in the GRADE assessment due to risk of bias and imprecision) indicated that immunoglobulins did not make a significant difference in reducing length of hospitalisation for children with RSV infection.

There was no difference in the number of children who experienced one or more adverse events (of any severity or seriousness) between the immunoglobulin and placebo groups based on evidence from five studies assessed as at low certainty (downgraded due to risk of bias and imprecision). There was no difference in the number of children who experienced one or more adverse events considered by study investigators to be serious in nature between the immunoglobulin and placebo groups based on evidence from three studies assessed as at low certainty (downgraded due to risk of bias and imprecision).

Low-certainty evidence (downgraded in the GRADE assessment due to risk of bias and imprecision) demonstrated that immunoglobulins did not make a significant difference in the need for or duration of mechanical ventilation, the need for or duration of supplemental oxygen, and the need for or duration of stay in the ICU compared to placebo. We identified no studies providing data on the effect of immunoglobulins on pulmonary function or the occurrence of reactive airway disease in the long term.

Overall completeness and applicability of evidence

Seven small studies (involving a total of 486 children) met the review inclusion criteria. Uncertainty about the effect of immunoglobulins on mortality reflects the small sample sizes and low event rates. For most comparisons, confidence intervals were very wide, and we could not rule out the possibility of clinically relevant differences. In some studies, outcome data were not always reported in a way that could be analysed, for example reporting of medians and absence of variation data.

All studies included hospitalised children with laboratory-confirmed RSV infection. All trials were conducted at sites in high-income countries (USA, Chile, New Zealand, Australia), with two studies including a site in a middle-income country (Panama). The applicability of findings to low- and middle-income countries, where rates of mortality from RSV infection are higher, is therefore unclear.

There was variation in the populations in the included studies (children were "previously healthy", were considered "high risk" for RSV infections, or had chronic medical conditions) and in the severity of illness at study entry (in two studies children were mechanically ventilated or required more than 30% supplemental oxygen). Given this variation, it is not clear if a specific group of children (i.e. those with more severe illness) might benefit from immunoglobulin treatment.

There was variation in the immunoglobulin preparations evaluated in the studies. Four studies evaluated different doses of the monoclonal immunoglobulins motavizumab (which is no longer available) and palivizumab. The remaining studies evaluated the pooled immunoglobulin respiratory syncytial virus immune globulin (RSVIG) (which was superseded by palivizumab). We were unable to perform further investigation of the effect of the alternate preparations in planned subgroup analysis due to the small number of included studies.

We identified an ongoing trial comparing a single dose of palivizumab with placebo in infants aged up to three months with RSV bronchiolitis (NCT02442427). A primary outcome of this review is readmission to either observation or hospital or paediatric ICU during three weeks of follow-up after discharge. Recruitment status is complete (last update posted 27 February 2018). This study will be assessed for inclusion and results presented in a future review update if appropriate.

The overall completeness and applicability of evidence was limited. There were few trials with small samples assessing the effects of immunoglobulins, predominantly in high-income healthcare settings.

Quality of the evidence

Using the GRADE methodology, which provides outcome-specific ratings of the certainty of evidence, we considered confidence

in the estimate of effect to be low or very low for the primary outcomes assessed in this review, due primarily to serious risk of bias and imprecision.

For the primary outcomes of the review (mortality, length of hospitalisation, and adverse events), we considered risk of bias to be serious due to unclear random sequence generation (all studies), allocation concealment (in some studies), and selective reporting (all studies). Furthermore, we considered all studies to be at risk of other bias because they were funded by parties with vested interest in the results, and/or trial authors or members of the study group had notable conflicts of interest.

We downgraded the quality of the evidence for the primary outcomes of the review due to imprecision. The effect estimate for mortality was derived from few small studies, a low event rate with wide confidence intervals including the null effect for appreciable harm or benefit. The evidence for length of hospitalisation and adverse events was also imprecise owing to small sample size compared to the calculated optimal information size, and wide confidence intervals. Consequently, the estimates of effect that have been presented should be considered uncertain, with further research likely to change these estimates.

Potential biases in the review process

We attempted to limit bias in the review process by following the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, there were several possible limitations of this review related to the process of selecting studies, extracting data, and assessing risk of bias. Although two review authors worked independently on each step, the second review authors varied between and within steps (i.e. the review authors screening the titles and abstracts of the original and updated searches may have been different, and different review authors acted as second reviewers for the risk of bias and data extraction steps). The effect of this on the outcomes and conclusions of the review is unclear. In addition, we did not attempt to obtain data from studies reporting unuseable outcome data. Although the search was thorough, it is possible that published and unpublished studies were not identified. The impact of possible omission on the results of the review is uncertain.

Agreements and disagreements with other studies or reviews

We are aware of only one other systematic review that has examined immunoglobulins as a treatment for RSV infection (Hu 2010). This review included studies of any design published to mid-2009 evaluating palivizumab in people of any age with RSV infection. The review included one case report, four case series, and two randomised trials (also included in this review). The primary outcomes were progression from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI) and survival. The methods of the search were provided, although the methods of selecting, extracting, and appraising studies were not reported. From the 7 included studies, Hu 2010 reported deaths in 3 of 25 (12%) participants with URTI receiving palivizumab and 5 of 88 (6%) participants with LRTI receiving palivizumab. The authors concluded that larger RCTs are required before palivizumab can be recommended as therapy for RSV.

AUTHORS' CONCLUSIONS

Implications for practice

Our review did not demonstrate that immunoglobulins improve important clinical outcomes for children younger than three years of age hospitalised with respiratory syncytial virus (RSV) infection. We found insufficient evidence of a difference between immunoglobulins and placebo for any review outcomes. We assessed the evidence for the effects of immunoglobulins when used as a treatment for RSV lower respiratory tract infection in hospitalised infants and young children as of low or very low certainty due to risk of bias and imprecision. We are uncertain of the effects of immunoglobulins on these outcomes, and the true effect may be substantially different from the effects reported in this review. All trials were conducted in high-income countries, and data from populations in which the rate of death from RSV infection is higher are lacking. Due to the low certainty of the evidence, cautious interpretation of the findings of this review is suggested.

Implications for research

Although there is no evidence of benefit in the studies included in this review, further research may consider studying the benefits and harms of immunoglobulins as a treatment for RSV in specific subgroups of children.

Given the substantial burden of RSV infection, and the lack of effective therapies at present, further research with newer monoclonal and pooled immunoglobulin preparations and in low-income countries may be considered. Such studies should be rigorously designed to minimise bias and assist applicability (e.g. by documenting when in the course of the illness treatment commenced).

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This review was based on a published review by Fuller 2006, which was withdrawn because the first author was unable to complete the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hemming 1987

Methods	**Study design:** parallel-group RCT **Setting:** children's hospital **Duration:** from recruitment to discharge variable. Follow-up 6 weeks and 1 year after discharge
Participants	**Location:** USA **Inclusion criteria** 1. Admitted for treatment of pneumonia or bronchiolitis 2. Were likely to be hospitalised for more than 4 days 3. Weighed 10 kg or less 4. Had nasal and pharyngeal swab specimens in which RSV antigens were detected by indirect immunofluorescence 5. Had informed consent by their parents **Exclusion criteria** 1. Congenital heart disease 2. Inability to establish an intravenous line 3. Failure to obtain informed consent from at least 1 parent 4. Previously known hypersensitivity to blood products **Baseline characteristics** (N = 35) Mean age (SD), months: treatment: 4.4 (4.3); comparator: 4.4 (4.1) Proportion male: not reported Health status/disease severity: not reported
Interventions	Treatment (N = 17): IV immunoglobulins containing high titres of RSV-neutralising antibody (geometric mean neutralising antibody titres of approximately 1:5000) 2 g/kg body weight administered over 12 to 24 hours Comparator (N = 18): placebo 2 g/kg body weight administered over 12 to 24 hours
Outcomes	1. Geometric mean titres of serum RSV-neutralising antibody and total IgG levels on day 1 following conclusion of infusion 2. Mean daily RSV titre reduction from baseline (expressed as 50% tissue culture infective dose per 0.2 mL log10) in nasal wash specimens on day 1 to 4 following conclusion of infusion 3. Increase or reduction from baseline in mean PO 2 oximetry values (mmHg) for study groups at day 1, 2, and 3 following conclusion of infusion 4. Supplemental oxygen requirements during hospitalisation (no details) 5. Duration of hospitalisation (days) 6. Duration of clinical symptoms such as sneezing, wheezing, rhonchi, rales, retractions, nasal discharge, or nasal obstruction (days)
Notes	This study was supported by the manufacturer of the immunoglobulin used in the study
Risk of bias	

Hemming 1987 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were assigned to 1 of 2 equal-size treatment groups based on a table of random numbers." (p. 1883) Comment: there was insufficient information on the method used to generate the randomisation sequence to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information on how the allocation sequence was concealed to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Only the study monitors (Sandoz Inc, East Hanover, NJ) knew the contents of the bottles of drug infused into each participant. The codes were not broken until the completion of each portion of the study." (p. 1883) "Lyophised human albumin, prepared in identical bottles and with protein concentrations identical to that of the IVIG, was used as the placebo drug." (p. 1882)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding of outcome assessment was not described. There is insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Complete 2 g/kg infusions were not completed in three patients, two IVIG treated and one placebo, because of problems maintaining venous access. IgG levels rose in both of these IVIG-treated children. .. suggesting receipt of most of the planned dose" (p. 1883) Comment: 35 participants were randomised. The number of participants not completing the study treatments was small (3 of 35), and analysis was based on all randomised participants for the outcomes RSV-neutralising antibody titres, IgG levels, and nasopharyngeal RSV infectivity titres. For the outcome of oximetry, only participants completing the infusion were included in the analysis (32/35). Follow-up was completed for 30 of the 35 children

Hemming 1987 (*Continued*)

		at 6 weeks and 1 year. The review authors judge that attrition is unlikely to have an important impact on the observed results
Selective reporting (reporting bias)	Unclear risk	Comment: outcomes were not specified in the methods section. Only a description of the tests carried out during hospitalisation was provided. The reporting of outcomes does not appear to be related to whether the results were significant or not, as both were presented. Also, without a trial protocol it is unclear if other outcomes were measured but not reported based on the nature of the results
Other bias	High risk	Quote: "This research was supported by Sandoz Pharmaceutical Corp." (p. 1885) (manufacturer of the IVIG used in this study) and the Children's Hospital National Medical Center. This may lead to bias in favour of the intervention group

Lagos 2009

Methods	**Study design:** parallel-group RCT **Setting:** hospital, not further described **Duration:** recruitment to discharge variable. Adverse events "monitored through study day 30". (p. 835)
Participants	**Location:** USA and Chile **Inclusion criteria** 1. Previously healthy children aged < 2 years and a gestational age ≥ 36 weeks 2. Hospitalised < 24 hours for RSV lower respiratory tract illness 3. RSV detected in respiratory secretions within the previous 72 hours by direct fluorescent antibody or rapid antigen detection **Exclusion criteria** 1. Children that had been treated with antiviral agents for the current RSV infection 2. Medically significant underlying illness 3. Previous supplemental oxygen use or mechanical ventilation 4. Use of palivizumab or other immunoglobulin products within the past 2 months **Baseline characteristics** Mean age (range), months: treatment: 7.6 (1.0 to 21.8); comparator: 7.4 (0.6 to 22.6) Proportion male: treatment 80%; comparator: 53% Health status/disease severity: children described as "previously healthy" (p. 835). Lower Respiratory Infection Score (6-point scale ranging from 0 = no respiratory infection to 5 = requiring mechanical ventilation): treatment: 2.5; comparator: 2.5

Interventions	Treatment (N = 5): single IV infusion of motavizumab at a dose of 3 mg/kg Treatment (N = 5): single IV infusion of motavizumab at a dose of 15 mg/kg Treatment (N = 5): single IV infusion of motavizumab at a dose of 30 mg/kg Dose escalation occurred after ≥ 7 days of safety follow-up of the previous dose group Comparator (N = 15): single IV infusion of 0.45% NaCl, which was identical in appearance to the motavizumab
Outcomes	1. Duration of hospitalisation (days) 2. Number of participants with > 1 instance of supplemental oxygen 3. Total duration of supplemental oxygen (days) 4. Number of participants admitted to ICU stay 5. Total duration of ICU stay (days) 6. Number of participants requiring mechanical ventilation 7. Total duration of mechanical ventilation (days) 8. Cultivatable RSV and viral RNA in nasal wash aspirates 9. RSV antigen in nasal secretions 10. Serum concentrations of motavizumab (μg/mL) 11. Adverse events and serious adverse events
Notes	This study was funded by the manufacturer of the immunoglobulin used in the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomised in 1:1 to groups..." (p. 835) Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "Participants were randomised in 1:1 to groups..." (p. 835) Comment: insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "...identically appearing placebo" (p. 835) Comment: insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All virologic assays were performed blind with respect to treatment assignment" (p. 835) Comment: blinding occurred for the RSV quantification outcomes (RSV quantification by viral culture and reverse transcriptase polymerase chain reaction), but blinding was not described for clinical outcomes.

Lagos 2009 (*Continued*)

		The risk of bias for the clinical outcomes is unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "thirty one children were randomised... Twenty-nine patients completed the study." (p. 836) Comment: 1 participant randomised to motavizumab was discontinued at day 0 because the study drug could not be administered within the protocol-specified time. 1 child was lost to follow-up at day 8 after dosing but was included in the analysis, so outcomes are reported for 30 of the 31 randomised participants. The small number (N = 1) and reason for missing outcome data is unlikely to have an important impact on the observed results
Selective reporting (reporting bias)	Unclear risk	Comment: outcome data are reported for all outcomes specified in the methods section of the publication. However, without a trial protocol it is unclear whether other outcomes were measured but not reported based on the nature of the results
Other bias	High risk	Quote: "This research was funded by MedImmune" (p. 835) (manufacturer of motavizumab), and several authors were employees of MedImmune. This may lead to bias in favour of the treatment group

Malley 1998

Methods	**Study design:** parallel-group RCT **Setting:** children's hospitals **Duration:** follow-up 30 days after administration of study treatments
Participants	**Location:** USA **Inclusion criteria** 1. < 24 months of age 2. RSV detected from respiratory secretions within 48 hours before randomisation by direct fluorescent antibody, IFA, ELISA, or culture 3. Intubation and conventional positive pressure ventilation for < 24 hours before randomisation **Exclusion criteria** 1. Intubation for apnoea only and requiring < 30% fraction of inspired oxygen 2. Significant cardiac abnormalities 3. Diagnosis of immunodeficiency

	4. Extracorporeal membrane oxygenation or high-frequency ventilation 5. Receipt of systemic steroids within 3 weeks before randomisation unless administered for the current RSV illness within 48 h before intubation 6. Use of oxygen for > 7 days in prior 3 months **Baseline characteristics** (N = 35) Median age (range), months: treatment: 3.2 (1.2 to 23.8); comparator: 1.7 (0.8 to 15.4) Proportion male: treatment: 59%; comparator: 72% Health status/disease severity: children required intubation and mechanical ventilation at study entry. 3 children (18%) in the treatment group and 3 children (17) in the comparator group had "significant chronic medical conditions at the time of randomization" (p. 1557). For the children in the treatment group, this included congenital anomalies in 1 child; microcephaly, developmental delay, and a seizure disorder in a second child; and a third child was quadriplegic. For the children in the comparator group, this included trisomy 21 in 2 children and Pierre Robin syndrome in 1 child
Interventions	Treatment (N = 17): intravenous palivizumab 15 mg/kg Comparator (N = 18): intravenous 0.9% saline
Outcomes	1. Reduction in tracheal RSV concentration from day 0 to day 1 and day 0 to day 2 2. RSV concentrations in nasal washes 3. White blood cell counts in tracheal aspirates 4. Days of hospitalisation 5. Days of mechanical ventilation 6. Total days of supplemental oxygen 7. Death
Notes	This study was funded by the manufacturer of the immunoglobulin used in the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: the method used to generate the allocation sequence is unclear. There was insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "The study was centrally randomized in blocks of six per site." (p. 1556) Comment: an adequate method to conceal the allocation sequence was likely used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All clinical and laboratory personnel, the participants, and families were blinded to the treatment assignment; the pharmacist at each site was unblinded." (p. 1556) Comment: it is likely that participants and caregivers were blinded

Malley 1998 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All clinical and laboratory personnel, the participants, and families were blinded to the treatment assignment; the pharmacist at each site was unblinded." (p. 1556) Comment: it is likely that the personnel responsible for outcome data were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All 35 randomized children were included in all analyses for which appropriate data were available." (p. 1557) Comment: all randomised children had data for clinical outcomes
Selective reporting (reporting bias)	Unclear risk	Comment: outcome data are reported for all outcomes specified in the methods section of the publication. However, without a trial protocol it is unclear whether other outcomes were measured but not reported based on the nature of the results
Other bias	High risk	Quote: "Financial support: MedImmune, Inc." (p. 1555) Comment: the trial was supported by MedImmune (manufacturer of MEDI-493). This may lead to bias in favour of the intervention group

Ramilo 2014

Methods	**Design:** multicentre, parallel-group, 3-arm RCT **Setting:** hospitals, not further described **Duration:** 1 year from randomisation to final follow-up
Participants	**Location:** "Northern and Southern Hemispheres", "5 countries". Trial registry indicates study sites in USA, Panama, Chile, New Zealand, and Australia **Inclusion criteria** 1. Previously healthy infants of ≥ 36 weeks gestational age 2. Aged ≤ 12 months 3. Hospitalised for LRTI with a documented positive RSV test **Exclusion criteria** 1. Receiving antiviral treatment for the current RSV infection 2. Use of steroids within 30 days of randomisation 3. Medically significant underlying illness 4. Intubation for ventilatory support, previous supplemental oxygen use, or mechanical ventilation at randomisation 5. Receipt of palivizumab or other immunoglobulin products during the 2 months before randomisation

	Baseline characteristics (N = 118) Median age (range), months: treatment: 2.0 (0.4 to 11.2) for the 30 mg/kg arm and 2.2 (0.3 to 11.3) for the 100 mg/kg arm; comparator: 2.7 (0.5 to 10.3) Proportion male: treatment: 51% for the 30 mg/kg arm and 51% for the 100 mg/kg arm; comparator: 73% Health status/disease severity: children were described as "previously healthy" (p. 703) . Median (range) Respiratory Distress Assessment Instrument (RDAI) score (17-point scale, with higher score indicating more severe wheezing and retractions): treatment: 6 (0 to 17) for the 30 mg/kg arm and 6 (0 to 13) for the 100 mg/kg arm; comparator: 4 (0 to 15)
Interventions	Treatment (N = 39): single IV dose of motavizumab 30 mg/kg Treatment (N = 39): single IV dose of motavizumab 100 mg/kg Comparator (N = 40): placebo (not further described)
Outcomes	1. RSV viral load in nasal wash specimens by reverse transcriptase polymerase chain reaction collected on days 0 to 6 (if still hospitalised), 7, 30, 90, 180 2. Duration of hospitalisation (days) 3. Supplemental oxygen use (number of study participants) and duration of use (days) 4. Mechanical ventilation use (number of study participants) and duration of use (days) 5. Admission to ICU (number of study participants) and duration of stay (days) 6. Adverse events 7. Wheezing episodes during 12-month follow-up
Notes	This study was sponsored by the manufacturer of the immunoglobulin used in the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible subjects were randomized to 1:1:1..." (p. 704) Comment: the method used to generate the allocation sequence is unclear. There is insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Eligible subjects were randomized to 1:1:1 using an interactive voice response system to receive... The interactive voice response system was also used for assignment of patient identification number and assignment of blinded study drug kits." (p. 704) Comment: an adequate method was used to conceal the allocation sequence

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...assignment of blinded study drug kits ...Subjects parents/guardians, clinical site staff and protocol-associated personnel were blinded to group assignment." (p. 704) Comment: it is likely that participants and care providers were blinded, although the appearance of the interventions is not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Subjects parents/guardians, clinical site staff and protocol-associated personnel were blinded to group assignment... At a central laboratory, personnel who were blinded to treatment assignment tested nasal specimens..." (p. 704) Comment: personnel responsible for the virologic and clinical outcome data were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 118 subjects were randomized... and 113 subjects received study drug. One hundred and seven subjects completed through study day 90 and 98 subjects completed through study day 360. Similar rates of non-completion were observed among subjects treated with motavizumab or placebo." (p. 704) Comment: 91% (107/118) of randomised participants remained in the study at day 90, with a similar number of non-completers in the study groups. Clinical outcome data are provided for 112 of 113 participants who received the study drug (1 participant was found to be negative for RSV at study day 0). Of the 112 participants with clinical outcome data, duration of hospitalisation data are available for 111 (1 participant in the motavizumab 30 mg/kg group withdrew consent). The review authors judge that the reasonably small number of participants randomised but not included in the analysis and the similar numbers lost to follow-up in the study groups is unlikely to have an important impact on the observed results

Ramilo 2014 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: outcome data were fully reported for all outcomes specified in ClinicalTrials.gov registry entry NCT00421304
Other bias	High risk	Quote: "This study was sponsored by MedImmune." (p. 703) Comment: the study was sponsored by MedImmune (the manufacturer of motavizumab), and a number of the study investigators received funding from or were employees of MedImmune. This may lead to bias in favour of the intervention group

Rodriguez 1997a

Methods	**Design:** multicentre, parallel-group RCT **Setting:** children's and university hospitals **Duration:** recruitment to discharge variable. Children were followed up in the next RSV season
Participants	**Location:** USA **Inclusion criteria** 1. High-risk infants and young children including those with severe bronchopulmonary dysplasia, other severe lung disease, or congenital heart disease and infants born prematurely (< 32 weeks' gestation who were < 6 months old at the time of enrolment) 2. Hospitalised for RSV bronchiolitis or pneumonia, or both, as defined by nasal specimens positive for RSV antigens by immunofluorescence or ELISA 3. Aged up to 2 years **Exclusion criteria** 1. Poorly controlled congestive heart failure before the RSV illness 2. Renal failure 3. Ventilator dependency before the RSV illness 4. Life expectancy of less than 6 months from study onset 5. Treatment with ribavirin before enrolment 6. Previous adverse reaction to blood products 7. Known serum immunoglobulin A deficiency or other immunodeficiency 8. Enrolment in a concurrent RSV immunoglobulin prophylaxis study 9. Patients with known cystic fibrosis, asthma, or reactive airway disease in the absence of bronchopulmonary dysplasia 10. Patients presenting with apnoea without evidence of lower tract infection **Baseline characteristics** (N = 102 (of 107 children randomised)) Mean age (SE), months: treatment: 0.55 (0.07); comparator: 0.58 (0.06) Proportion male: treatment: 45%; comparator: 57% Health status/disease severity: children were described as high risk for severe RSV infection. High-risk children included those with severe bronchopulmonary dysplasia, chronic lung disease, congenital heart disease, or prematurity. Mean (SE) respiratory score (score

Rodriguez 1997a (*Continued*)

	ranges from 0 to 5, with higher scores indicating more severe disease): treatment: 3.4 (0.2); comparator: 3.1 (0.1). Proportion with Lower Respiratory Tract Infection Score 5 (score ranges from 0 to 5, with 5 indicating respiratory failure): treatment: 31%; comparator: 18%
Interventions	Treatment (N = 54): 30 mL/kg RSVIG (1.5 mg/kg IVIG) given intravenously over 12 hours Comparator (N = 54): 0.15 mg/kg of albumin given intravenously over 12 hours
Outcomes	**Primary** 1. Duration of hospital stay (days) **Secondary** 1. Duration of ICU stay (days) 2. Duration of mechanical ventilation (days) 3. Duration of oxygen therapy (days) 4. Use of ribavirin 5. Use of supplemental oxygen
Notes	Some members of the study group were employees of the manufacturer of the immunoglobulin used in the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the method used to generate the allocation sequence is unclear. There was insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Each year of the study, MPHBL coded vials by one of six letters... Only MPHBL and the Data and Safety Monitoring Board member knew the contents of the vials until the study code was broken. .. Each centre received from MedImmune Inc a randomization schedule that ensured that each center enrolled nearly equal numbers of RSVIG and placebo patients by balancing randomisation in blocks of six. Patients who fit the inclusion criteria were assigned to the next lettered vial specified in the randomizations scheme for each centre. " (p. 456) Comment: an adequate method was likely used to conceal the allocation sequence

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Bottles containing respiratory syncytial virus immunoglobulin or placebo were coded by the MPHBL so that contents were unknown to the investigators, sponsor, and study participants... A 0.5% solution of albumin bottled identically to the RSVIG was used as the placebo solution." (p. 456) Comment: it is likely that participants and care providers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Bottles containing respiratory syncytial virus immunoglobulin or placebo were coded by the MPHBL so that contents were unknown to the investigators, sponsor, and study participants... A 0.5% solution of albumin bottled identically to the RSVIG was used as the placebo solution... Attending physicians not associated with the study were responsible for routine treatment... Furthermore, they determined when to administer supplemental oxygen, the level of oxygen therapy, or the need for mechanical ventilation. Likewise, the decision for hospital discharge was made by the attending physicians." (p. 456) Comment: it is likely that the personnel responsible for outcome data were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fifty four patients were randomized to receive RSVIG, and 53 were randomized to receive placebo. Three children in the RSVIG group and 2 in the placebo group received less than 75% of the ordered dose and those were not evaluable for efficacy." (p. 457) Comment: the review authors judge that owing to the small number of participants not completing study treatments and excluded from the analysis, the similar numbers in each study group, and for reasons unlikely to be related to the outcomes, this is unlikely to have an important impact on the observed results
Selective reporting (reporting bias)	Unclear risk	Comment: outcome data are reported for all outcomes specified in the methods section of the publication. However, without a trial protocol it is unclear whether other

Rodriguez 1997a (*Continued*)

		outcomes were measured but not reported based on the nature of the results
Other bias	Unclear risk	Quote: "This work was supported by grant H5 MO1RR0069, General Clinical Research Centers program, from the National Institutes of Health (University of Colorado)." (p. 460) Comment: a number of members of the RSVIG Study Group were employees of MedImmune (manufacturer of RSVIG). This may lead to bias in favour of the intervention group

Rodriguez 1997b

Methods	**Design:** multicentre, parallel-group RCT **Setting:** children's and university hospitals **Duration:** recruitment to discharge variable. Follow-up 8 weeks after discharge and during the following respiratory season
Participants	**Location:** USA **Inclusion criteria** 1. Previously healthy children ≤ 2 years of age 2. Hospitalised for bronchiolitis or pneumonia, or both, who are positive for RSV antigen by immunofluorescence or ELISA 3. Had acute lower respiratory symptoms less that 4 days' duration 4. Had a respiratory score ≥ 2.5 **Exclusion criteria** 1. Known or suspected cardiopulmonary disease 2. Premature birth (< 32 weeks) 3. Immunodeficiency disease 4. Renal failure 5. Previous reaction to blood products or having received blood products in the preceding 60 days 6. Established diagnosis of reactive airways disease 7. Apnoea without evidence of lower tract infection 8. Inability to establish intravenous line (4 attempts maximum) **Baseline characteristics** (N = 101) Mean age (SE), months: treatment: 0.20 (0.03); comparator: 0.19 (0.03) Proportion male: treatment 48%; comparator 50% Health status/disease severity: children were described as "previously healthy" (p. 938) . Mean (SE) Respiratory score (score ranges from 0 to 5, with higher scores indicating more severe disease): treatment: 3.69 (0.13); comparator: 3.77 (0.13). Proportion with Lower Respiratory Tract Infection Score 5 (score ranges from 0 to 5, with 5 indicating respiratory failure): treatment: 28%; comparator: 33%

Rodriguez 1997b (*Continued*)

Interventions	Treatment (N = 47): 30 mL/kg (1500 mg/kg) infusion of RSVIG Comparator (N = 54): 30 mL/kg (1500 mg/kg) infusion of albumin placebo
Outcomes	**Primary** 1. Duration of hospitalisation (days) **Secondary** 1. Duration of stay in the ICU (days) 2. Duration of mechanical ventilation (days) 3. Duration of oxygen therapy (days) 4. Use of ribavirin 5. Supplemental oxygen **Other** 1. Respiratory score (used as an inclusion criterion and to conduct stratified analyses in the study) 2. Lower Respiratory Infection score (clinical investigator's assessment of participants) 3. Analogue scale of disease severity (visual disease severity scoring system)
Notes	This study was supported by the manufacturer of the immunoglobulin used in the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the method used to generate the allocation sequence is unclear. There was insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "Bottles containing RSVIG or placebo were coded by the Massachusetts Public Health Biological Laboratories so that controls were unknown to investigators, sponsor and study participants." (p. 938) Comment: there was insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A one half percent (0.5%) solution of albumin bottled identically to the RSBIG was utilized as the placebo control solution." (p. 938) Comment: it is likely that participants and care providers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Bottles containing respiratory syncytial virus immunoglobulin or placebo were coded by the Massachusetts Public

		Health Biological Laboratories so that contents were unknown to the investigators, sponsor, and study participants. ...A 0.5% solution of albumin bottled identically to the RSVIG was used as the placebo solution... Attending physicians determined whether and when supplemental oxygen or mechanical ventilation was required. The decision for hospital discharge was also made by the attending physicians." (p. 938) Comment: it is likely that the personnel responsible for the primary and secondary outcome data were blinded. It is unclear who evaluated participants by the analogue scale, LRI, and respiratory score and if they were blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One hundred one patients were enrolled in the trial, 47 in the RSVIG group and 54 in the placebo group. Forty-six RSVIG (98%) and 52 placebo recipients (96%) could be evaluated. Excluded from the evaluation were 1 infant in the RSVIG group who received less than 75% of the infusion, 1 placebo recipient who had an admission respiratory score < 2.5, and 1 placebo patient on whom we were unable to start an intravenous infusion." (p. 939) Comment: the review authors judge that owing to the small number of participants not completing study treatments and excluded from the analysis, the similar numbers in each study group, and for reasons unlikely to be related to the outcomes, this is unlikely to have an important impact on the observed results
Selective reporting (reporting bias)	Unclear risk	Comment: outcome data are reported for all outcomes specified in the methods section of the publication. However, without a trial protocol it is unclear whether other outcomes were measured but not reported based on the nature of the results
Other bias	High risk	Quote: "This study was supported by MedImmune, Inc. and by Grant H5 MO1RR0069, General Clinical Research Centers Program National Institutes of Health (University of Colorado)." (p. 941) Comment: the study is supported in part by

Rodriguez 1997b (*Continued*)

		MedImmune, and a number of members of the RSVIG Study Group are employees of MedImmune (manufacturer of RSVIG) . This may lead to bias in favour of the intervention group

Sáez-Llorens 2004

Methods	**Design:** multicentre, parallel-group RCT **Setting:** hospitals, not further described **Study duration:** follow-up for 30 days after study drug administration and during the following RSV season
Participants	**Location:** USA and Panama **Inclusion criteria** 1. ≤ 24 months of age at the time of randomisation 2. Hospitalised within 72 hours before randomisation into the study for RSV bronchiolitis or pneumonia, or both, as documented by antigen detection in nasopharyngeal or lower respiratory tract secretions collected within 48 hours before randomisation 3. Required > 30% supplemental oxygen **Exclusion criteria** 1. Therapy with ribavirin for the current illness before randomisation 2. Significant underlying chronic or acute disease other than the RSV infection (e.g. bronchopulmonary dysplasia) 3. Known renal, hepatic, haematologic, neurologic, or immunologic disorder 4. Requirement for supplemental oxygen in the past 6 months (brief oxygen use at birth, oxygen use of < 1 week to treat an intercurrent illness, or need for oxygen or mechanical ventilation during the current RSV infection was allowed) 5. Mechanical ventilation at any time before the onset of the current RSV infection 6. Congenital heart disease (except corrected patent ductus arteriosus with no other congenital heart disease) 7. Previous reaction to immunoglobulin, blood products, or other foreign proteins 8. Previous treatment with any immunoglobulin product within the past 2 months 9. Therapy with any other investigational agent currently or within the past 3 months 10. Previous or current participation in any investigational study of vaccines or immunotherapeutic agents for RSV **Baseline characteristics** (N = 59) Mean age (SE), months: treatment: 1.5 (0.4) for palivizumab 5 mg/kg arm and 5.2 (0.9) for palivizumab 15 mg/kg arm; comparator: 2.9 (0.7) for the group compared to palivizumab 5 mg/kg arm and 4.2 (0.8) for the group compared to palivizumab 15 mg/kg arm Proportion male: treatment: 75% for palivizumab 5 mg/kg arm and 59% for palivizumab 15 mg/kg arm; comparator: 13% for the group compared to palivizumab 5 mg/kg arm and 48% for the group compared to the palivizumab 15 mg/kg arm Health status/disease severity: children described as “previously healthy” (p. 707). Children required > 30% supplemental oxygen at study entry. Proportion with Lower Res-

	piratory Infection score ≥ 3 (score ranges from 0 to 5, with 0 indicating no respiratory illness, 3 indicating moderate lower respiratory infection, and 5 indicating the need for mechanical ventilation): treatment: 100% for palivizumab 5 mg/kg arm and 36% for palivizumab 15 mg/kg arm; comparator: 88% for the group compared to palivizumab 5 mg/kg arm and 33% for the group compared to palivizumab 15 mg/kg arm
Interventions	Treatment (N = 8): 5 mg/kg intravenous palivizumab Treatment (N = 22): 15 mg/kg intravenous palivizumab. The dose of palivizumab was increased to 15 mg/kg after the first 12 children receiving the 5 mg/kg dose had been followed for at least 5 days after treatment without the occurrence of dose-limiting toxicity or serious adverse event Comparator (N = 29): placebo (0.9% normal saline)
Outcomes	1. Adverse events 2. Serum palivizumab concentrations (before administration of study drug, 60 minutes after infusion, and 2, 5, 14, and 30 days after infusion) (for intervention group only and comparing participants receiving doses of 5 mg/kg and 15 mg/kg palivizumab) 3. Duration of hospitalisation (days) 4. Hospital days of supplemental oxygen therapy 5. RSV hospitalisation days with LRI score ≥ 3
Notes	Members of the study group were employees of the manufacturer of the immunoglobulin used in the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomized centrally 1:1..." (p. 707) Comment: although randomisation appeared to be independent of study investigators, the way the sequence was generated was not described. There was insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Eligible patients were randomized 1:1 centrally by the investigator calling Pharmaceutical Products Development Inc. and obtaining the next available patient identification number with specified study drug." (p. 707) Comment: an adequate method was likely used to conceal the allocation sequence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study drug was dispensed from the pharmacy in a blinded manner; i.e., the study drug assignment was not on

		the label" (p. 708) Comment: it is likely that participants and care providers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Adverse events considered by the blinded investigator to be possibly related. .." (p. 710) Comment: the study states that adverse events were classified by a blind investigator, however it is unclear whether clinical outcomes were reported by blind clinicians, and the risk of detection bias is unclear for these outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 60 children were randomized and 59 received the study drug. One child was randomized but did not receive any study drug because of a protocol violation: this patient was not included in any of the analyses... Overall 56 patients (95%) were followed through 30 days after study drug administration. One placebo patient died during RSV hospitalisation and 2 patients, one placebo and the other 15 mg/kg palivizumab were lost to follow-up during the 30 day post treatment period" (p. 709) Comment: only 1 randomised participant was not included in the analysis for adverse events and clinical outcomes, and this was due to a protocol violation. Attrition in this study is unlikely to have an important impact on the observed results
Selective reporting (reporting bias)	Unclear risk	Comment: outcome data are reported for all outcomes specified in the methods section of the publication. However, without a trial protocol it is unclear whether other outcomes were measured but not reported based on the nature of the results
Other bias	Unclear risk	Quote: "We thank Barbara Shepherd, PhD of MedImmune, Inc. for assistance with preparation of the manuscript" (p. 712) Comment: the paper acknowledges an employee of MedImmune (palivizumab manufacturer) for assistance with preparation of the manuscript. A member of the MEDI-493 Study Group is an employee of Med-

		Immune. This may lead to bias in favour of the intervention group

ELISA: enzyme-linked immunosorbent assay
ICU: intensive care unit
IFA: immunofluorescence assay
IgG: immunoglobulin G
IV: intravenous
IVIG: intravenous immunoglobulins
LRI: lower respiratory infection
LRTI: lower respiratory tract infection
N: number (of people)
NaCl: normal saline
PO_2 : partial pressure of oxygen
RCT: randomised controlled trial
RNA: ribonucleic acid
RSV: respiratory syncytial virus
RSVIG: respiratory syncytial virus immunoglobulins
SD: standard deviation
SE: standard error

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AAP 1998	Not an RCT (review)
Faber 2008	Not an RCT (review)
Feltes 2011	This study looked at prophylaxis, not treatment.
Fernández 2010	This study looked at prophylaxis, not treatment.
Givner 1999	Not an RCT (review)
Halsey 1997	This study looked at prophylaxis, not treatment.
Harkensee 2006	Not an RCT (review)
Helmink 2016	This study did not randomise participants to palivizumab or control
Hu 2010	Not an RCT (review)
Wegzyn 2014	Not an RCT (review)

RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT02442427

Trial name or title	Palivizumab therapy for RSV-bronchiolitis
Methods	Randomised placebo-controlled trial
Participants	Infants 3 years of age or younger presenting to an emergency department with acute bronchitis and positive RSV rapid antigen test
Interventions	Single-dose intravenous palivizumab versus saline placebo comparator
Outcomes	Readmission during 3-week follow-up after discharge
Starting date	September 2014
Contact information	Information provided by: Hamad Medical Corporation
Notes	Sponsor: Hamad Medical Corporation

RSV: respiratory syncytial virus

DATA AND ANALYSES

Comparison 1. Immunoglobulins versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (any cause during hospitalisation or follow-up)	3	196	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.14, 5.27]
2 Length of hospitalisation (days)	5	324	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.83, 0.42]
3 Adverse events of any severity or seriousness	5	340	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.78, 1.78]
4 Serious adverse events	4	238	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.65, 1.79]
5 Need for mechanical ventilation	4	341	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.64, 2.41]
6 Duration of mechanical ventilation	3	100	Mean Difference (IV, Random, 95% CI)	-0.22 [-2.64, 2.21]
7 Need for supplemental oxygen	2	142	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.94, 1.49]
8 Duration of supplemental oxygen	3	115	Mean Difference (IV, Random, 95% CI)	-0.54 [-2.26, 1.17]
9 Need for ICU admission	4	341	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.64, 2.32]
10 Duration of stay in the ICU	2	107	Mean Difference (IV, Random, 95% CI)	-2.13 [-4.55, 0.30]

Analysis 1.1. Comparison 1 Immunoglobulins versus placebo, Outcome 1 Mortality (any cause during hospitalisation or follow-up).

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 1 Mortality (any cause during hospitalisation or follow-up)

Study or subgroup	Ig n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
S ez-Llorens 2004	0/30	1/29		32.1 %	0.32 [0.01, 7.61]
Malley 1998	0/17	1/18		32.6 %	0.35 [0.02, 8.09]
Rodriguez 1997a	2/51	0/51		35.3 %	5.00 [0.25, 101.63]
Total (95% CI)	**98**	**98**		**100.0 %**	**0.87 [0.14, 5.27]**

Total events: 2 (Ig), 2 (Placebo)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.02$, df = 2 (P = 0.36); $I^2 = 1\%$

Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Immunoglobulins versus placebo, Outcome 2 Length of hospitalisation (days).

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

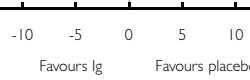
Outcome: 2 Length of hospitalisation (days)

Study or subgroup	Ig		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Malley 1998	17	14.5 (8.7)	18	11.5 (6.4)		4.9 %	3.00 [-2.08, 8.08]
Lagos 2009	15	4.9 (5.2)	15	6.8 (7.4)		6.0 %	-1.90 [-6.48, 2.68]
Rodriguez 1997a	51	8.4 (6.9)	51	8.8 (7.1)		17.1 %	-0.40 [-3.12, 2.32]
S ez-Llorens 2004	30	4.4 (4.5)	29	5.4 (5.6)		18.8 %	-1.00 [-3.60, 1.60]
Rodriguez 1997b	46	4.6 (2.7)	52	5.5 (4.9)		53.1 %	-0.90 [-2.44, 0.64]
Total (95% CI)	**159**		**165**			**100.0 %**	**-0.70 [-1.83, 0.42]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.46$, df = 4 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: Not applicable

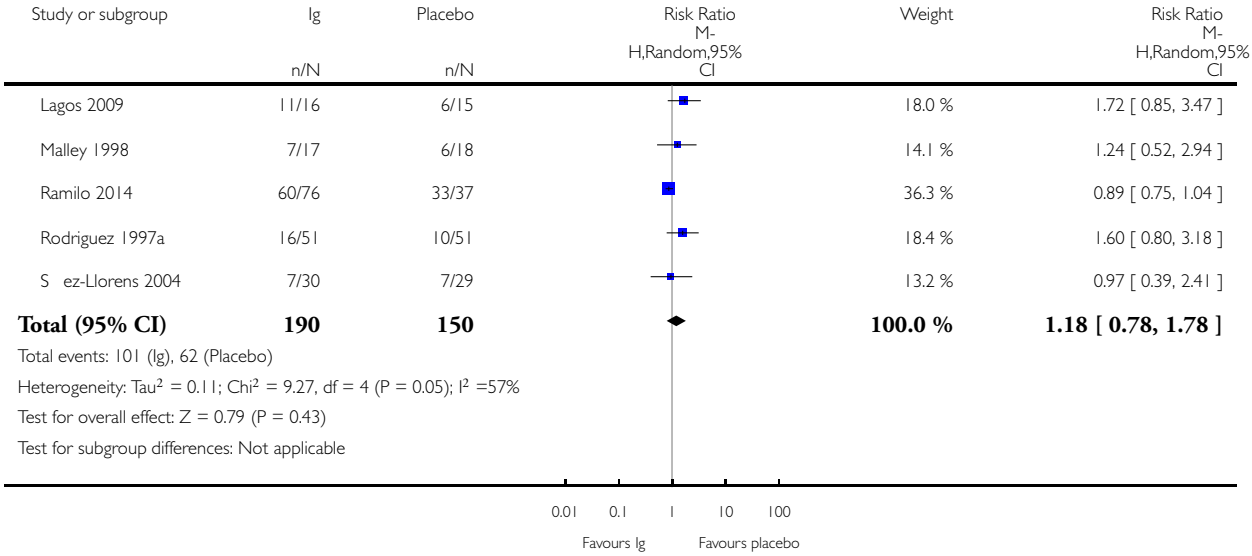


Analysis 1.3. Comparison 1 Immunoglobulins versus placebo, Outcome 3 Adverse events of any severity or seriousness.

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 3 Adverse events of any severity or seriousness



Analysis 1.4. Comparison 1 Immunoglobulins versus placebo, Outcome 4 Serious adverse events.

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 4 Serious adverse events

Study or subgroup	Ig n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lagos 2009	1/16	1/15		3.5 %	0.94 [0.06, 13.68]
Malley 1998	7/17	6/18		33.8 %	1.24 [0.52, 2.94]
Ramilo 2014	13/76	6/37		32.4 %	1.05 [0.44, 2.55]
S ez-Llorens 2004	7/30	7/29		30.3 %	0.97 [0.39, 2.41]
Total (95% CI)	**139**	**99**		**100.0 %**	**1.08 [0.65, 1.79]**

Total events: 28 (Ig), 20 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.16$, df = 3 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 0.30 (P = 0.77)

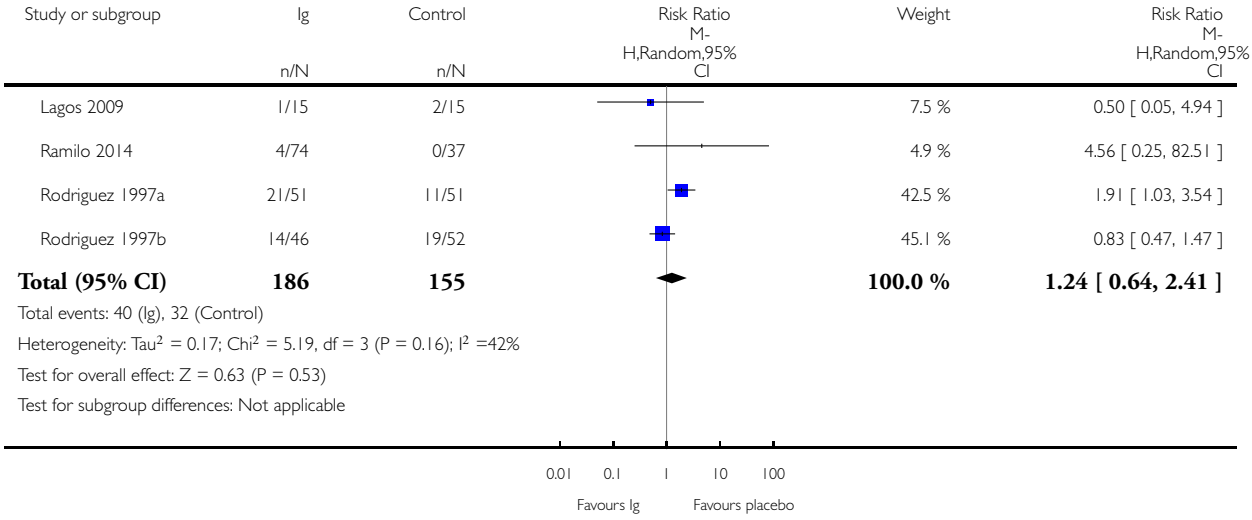
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Immunoglobulins versus placebo, Outcome 5 Need for mechanical ventilation.

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 5 Need for mechanical ventilation

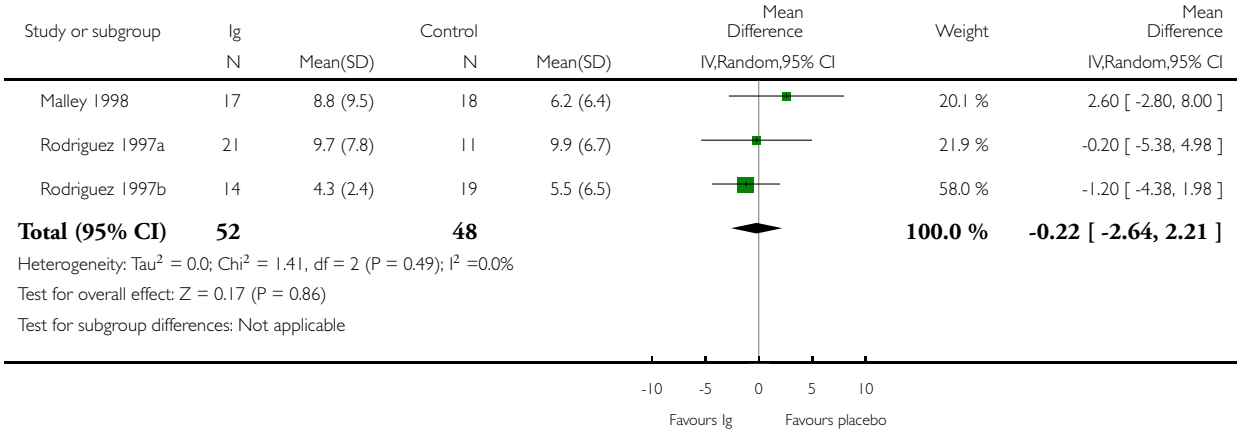


Analysis 1.6. Comparison 1 Immunoglobulins versus placebo, Outcome 6 Duration of mechanical ventilation.

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 6 Duration of mechanical ventilation

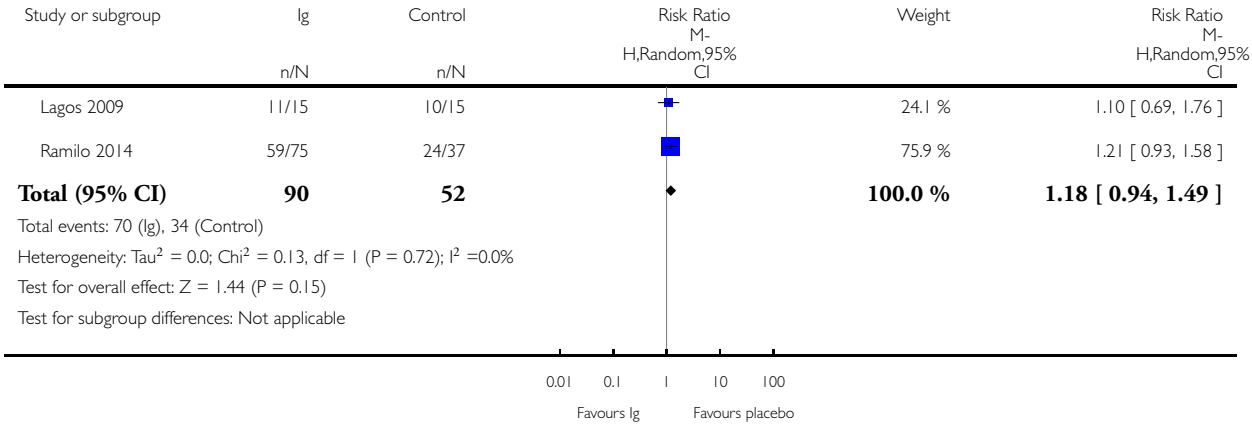


Analysis 1.7. Comparison 1 Immunoglobulins versus placebo, Outcome 7 Need for supplemental oxygen.

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 7 Need for supplemental oxygen

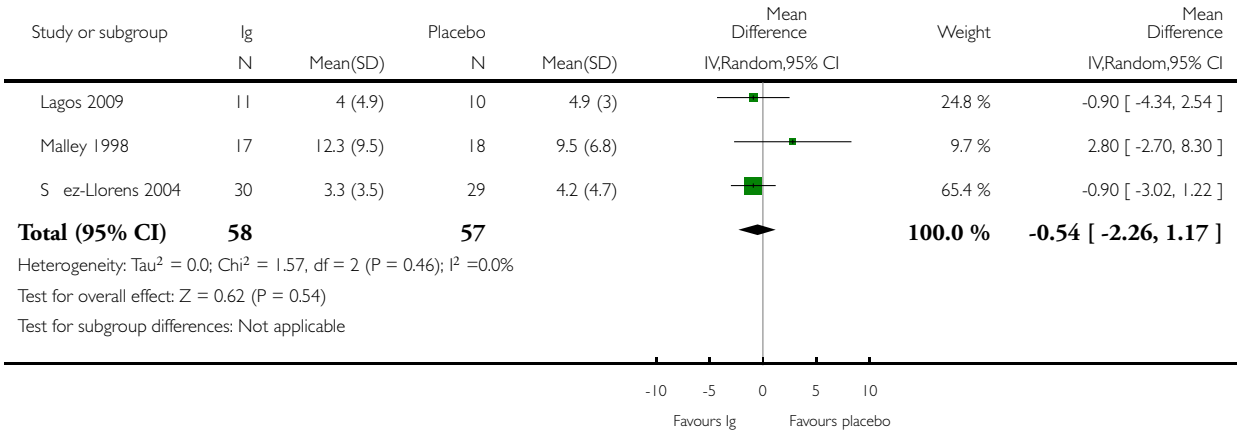


Analysis 1.8. Comparison 1 Immunoglobulins versus placebo, Outcome 8 Duration of supplemental oxygen.

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 8 Duration of supplemental oxygen

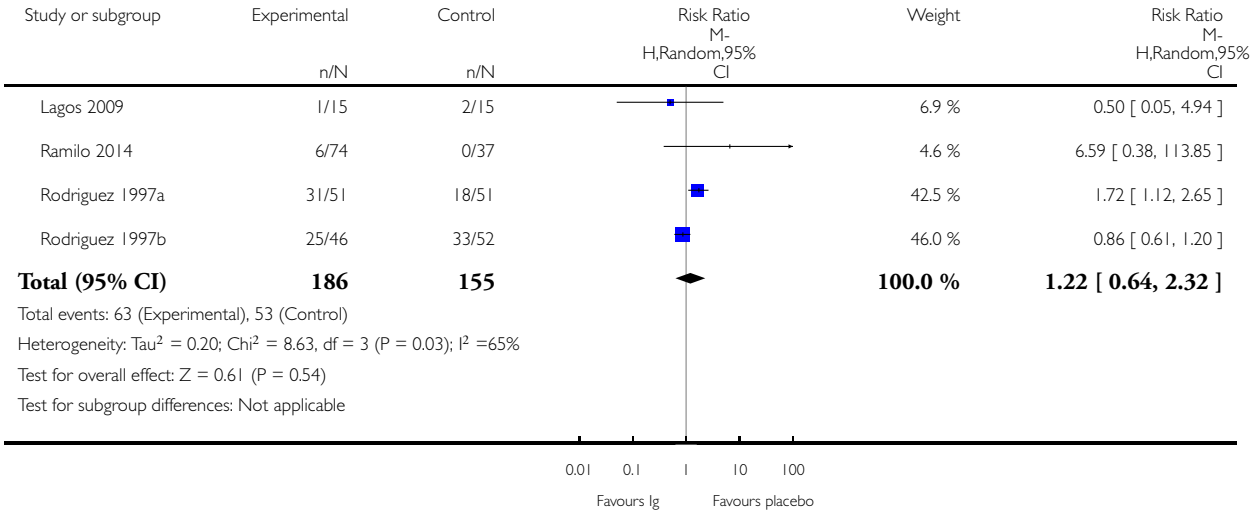


Analysis 1.9. Comparison 1 Immunoglobulins versus placebo, Outcome 9 Need for ICU admission.

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 9 Need for ICU admission

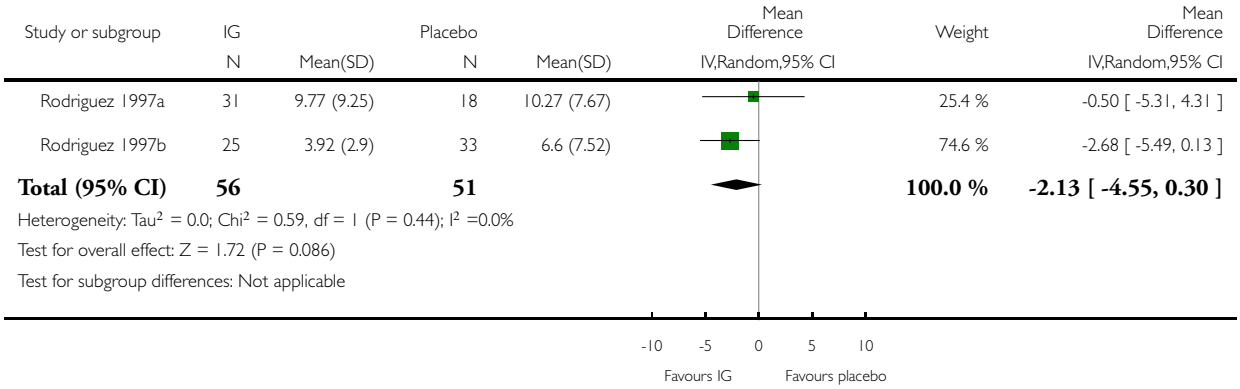


Analysis 1.10. Comparison 1 Immunoglobulins versus placebo, Outcome 10 Duration of stay in the ICU.

Review: Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection

Comparison: 1 Immunoglobulins versus placebo

Outcome: 10 Duration of stay in the ICU



ADDITIONAL TABLES

Table 1. Mortality from any cause during hospitalisation or follow-up

Study	Number of deaths in the immunoglobulin group	Immunoglobulin group total	Number of deaths in the placebo group	Placebo group total
Hemming 1987	1 death (study group unknown)			
Malley 1998	0	17	1	18
Rodriguez 1997a	2	51	0	50
Sáez-Llorens 2004	0	30	1	29

Table 2. Adverse events

Study	Number of children/total number in group (%) experiencing ≥ 1 adverse event	Number of children/total number in group (%) experiencing ≥ 1 adverse event judged by study investigators to be serious in nature	Number of participants/total number in group (%) experiencing ≥ 1 adverse event judged by study investigators to be related to study drug	Narrative results provided by the study investigators

Table 2. Adverse events (*Continued*)

	Immunoglobulin	Placebo	Immunoglobulin	Placebo	Immunoglobulin	Placebo	
Lagos 2009	11/16 (69)	6/15 (40)	1/16 (6)	1/15 (7)	0	0	"The frequency of AEs was similar between the combined motavizumab groups and the placebo group" (p. 836)
Ramilo 2014	60/76 (79)	33/37 (89)	13/76 (17)	6/37 (16)	6/76 (8)	4/37 (11)	"The incidence rates of AEs and SAEs were similar for the 3 groups" (p. 706)
Rodriguez 1997a	16/51 (31)	10/51 (20)	NA	NA	16 of 22 adverse events among the 16 immunoglobulin participants experiencing ≥ 1 adverse event and 8 of 11 adverse events among 10 placebo participants experiencing ≥ 1 adverse event were judged to be related to study drug		"No significant differences in adverse events were reported in the RSVIG group... when compared with the control group" (p. 454)
Malley 1998	NA	NA	7/17 (41)	6/18 (33)	0	0	"The percentage of children reporting adverse events and the total number of adverse events were similar in the placebo and MEDI0493 groups" (p. 1559)
Sáez-Llorens 2004	NA	NA	7/30 (23)	7/29 (24)	1/30 (3)	3/30 (10)	"The incidence of individual adverse events was balanced between the placebo and palivizumab treatment groups for each dose" (p. 710)

AE: adverse event, NA: not available, RSVIG: respiratory syncytial virus immunoglobulin, SAE: serious adverse event

APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

MEDLINE (Ovid)

1 exp Bronchiolitis/
2 bronchiolit*.tw.
3 exp Pneumonia/
4 (pneumon* or bronchopneumon* or pleuropneumon*).tw.
5 Respiratory Tract Infections/
6 lower respiratory infection*.tw.
7 (lower respiratory tract infection* or lrti).tw.
8 respiratory syncytial viruses/ or respiratory syncytial virus, human/
9 Respiratory Syncytial Virus Infections/
10 (respiratory syncytial virus* or rsv).tw.
11 or/1-10
12 exp Immunoglobulins/
13 immunoglobulin*.tw,nm.
14 (immune adj2 globulin*).tw.
15 rsv-igiv.tw,nm.
16 respigam.tw,nm.
17 palivizumab.tw,nm.
18 synagis.tw,nm.
19 or/12-18
20 11 and 19

Appendix 2. Embase (Elsevier) search strategy

#19 #15 AND #18
#18 #16 OR #17
#17 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR (((singl* OR doubl*) NEXT/1 blind*):ab,ti)
#16 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#15 #9 AND #14
#14 #10 OR #11 OR #12 OR #13
#13 'rsv-igiv':ab,ti OR respigam:ab,ti OR palivizumab:ab,ti OR synagis:ab,ti
#12 (immune NEAR/2 globulin*):ab,ti
#11 immunoglobulin*:ab,ti
#10 'immunoglobulin'/exp
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#8 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti
#7 'respiratory syncytial pneumovirus'/de OR 'respiratory syncytial virus infection'/de
#6 'lower respiratory tract infection':ab,ti OR 'lower respiratory tract infections':ab,ti OR 'lower respiratory infection':ab,ti OR 'lower respiratory infections':ab,ti OR lrti:ab,ti
#5 'respiratory tract infection'/de OR 'lower respiratory tract infection'/exp
#4 pneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleuropneumon*:ab,ti
#3 'pneumonia'/exp
#2 bronchiolit*:ab,ti
#1 'bronchiolitis'/exp

Appendix 3. CINAHL (EBSCO) search strategy

S26 S16 and S25 59
S25 S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24
S24 (MH "Quantitative Studies")
S23 (MH "Placebos")
S22 TI placebo* OR AB placebo*
S21 TI random* OR AB random*
S20 TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*))
S19 TI clinic* trial* OR AB clinic* trial*
S18 PT clinical trial
S17 (MH "Clinical Trials+")
S16 S10 and S15
S15 S11 or S12 or S13 or S14
S14 TI (rsv-igiv or respigam or palivizumab or synagis) OR AB (rsv-igiv or respigam or palivizumab or synagis)
S13 TI immune N2 globulin* OR AB immune N2 globulin*
S12 TI immunoglobulin* OR AB immunoglobulin*
S11 (MH "Immunoglobulins+")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 16135
S9 TI (respiratory syncytial virus* or rsv) OR AB (respiratory syncytial virus* or rsv)
S8 (MH "Respiratory Syncytial Virus Infections")
S7 (MH "Respiratory Syncytial Viruses")
S6 TI (lower respiratory tract infection* or lower respiratory infection* or lrti) OR AB (lower respiratory tract infection* or lower respiratory infection* or lrti)
S5 (MH "Respiratory Tract Infections")
S4 TI pneumon* OR AB pneumon*
S3 (MH "Pneumonia+")
S2 TI bronchiolit* OR AB bronchiolit*
S1 (MH "Bronchiolitis+")

Appendix 4. Web of Science (Clarivate Analytics) search strategy

TOPIC: ((bronchiolit* or pneumon* or bronchopneumon* or pleuropneumon* or "lower respiratory tract infection*" or "lower respiratory infection*" or lrti or rsv or "respiratory syncytial virus" or "respiratory syncytial viruses")) *AND* TOPIC: ((immunoglobulin* or "immune globulin" or "rsv-igiv" or respigam or palivizumab or synagis))
Refined by: TOPIC: ((random* or placebo* or "clinic* trial*" or "singl* blind*" or "doubl* blind*"))
Timespan: All years. Indexes: SCI-EXPANDED, CPCI-S.

CONTRIBUTIONS OF AUTHORS

Sharon L Sanders: screened searches, extracted data, assessed risk of bias, analysed results, and drafted the final review

Sushil Agwan: extracted data, verified data entry, drafted sections of the final review, and reviewed draft

Mohamed Hassan: extracted data, verified data entry, drafted sections of the final review, and reviewed draft

Mieke L van Driel: screened searches, extracted data, assessed risk of bias, and reviewed draft

Chris B Del Mar: screened searches, extracted data, assessed risk of bias, and reviewed draft

DECLARATIONS OF INTEREST

Sharon L Sanders: none known

Sushil Agwan: none known

Mohamed Hassan: none known

Mieke L van Driel: none known

Chris B Del Mar: none known

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- No external funding received, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

New authors joined the review (SLS, SA, and MH).

We made several changes to the secondary outcomes specified in the protocol. We changed adverse effects of the treatments from being a secondary outcome in the protocol to a primary outcome in the review. The protocol also specified secondary outcomes related to the duration of ventilation and attendance in the intensive care unit. We included the secondary outcome "need for ventilation" in addition to the existing "duration of ventilation" outcome in the review. We included the secondary outcome "need for intensive care unit admission" and renamed the outcome "days admitted to the intensive care unit" to "duration of stay in the intensive care unit". We renamed the secondary outcome "oxygen dependence" to "need for supplemental oxygen" and "duration of supplemental oxygen". We added the secondary outcomes related to need for mechanical ventilation, supplemental oxygen, and intensive care unit admission, as we felt these were patient-important outcomes. We also identified the limitation in duration-related outcomes. Duration data were only available for those children requiring mechanical ventilation, supplemental oxygen, or intensive care admission. This means the comparisons between the interventions (immunoglobulins and placebo) were not randomised comparisons, and the outcomes are at risk of selection bias. The need for ventilation, supplemental oxygen, and intensive care unit admission outcomes are randomised comparisons.

We used GRADE to assess the certainty of the body of evidence and included a 'Summary of findings' table. We did not contact trial authors for missing trial information or unpublished studies as was intended when the protocol was written due to resource constraints.

Missing data due to losses to follow-up or protocol deviation were minimal; we took missing data into account in the 'Risk of bias' assessment and did not apply any imputation measures as intended in the protocol. We expressed dichotomous outcomes as risk ratios rather than odds ratios as stated in the protocol for their ease of interpretation.

We were unable to conduct prespecified subgroup analysis due to lack of data.